PCT/EP03/13085

Rec'd PCT/PTO 20 MAY 2005

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

REC'D 09 FEB 2004
WIPO PCT

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

Signed Stephen Hordley

Dated 21 November 2003

Patents Form 1/77

Patents Act 1977
(Rule 16)

The Patent Office

22NOV02 E765435-1 D02029
P01/7700 0.00-0227240.9

1/77

THE PATENT OFFICE
B
21 NOV 2002
LONDON

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
Gwent NP9 1RH

1. Your Reference — **RK/P33150**

2. Patent application number *(The Patent office will fill in this part)* — 0227240.9 — 21 NOV 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

GLAXO GROUP LIMITED
GLAXO WELLCOME HOUSE
BERKELEY AVENUE
GREENFORD
MIDDLESEX
UB6 ONN
GB

Patents ADP number *(if you know it)* 08202293001

If the applicant is a corporate body, give the country/state of its corporation — **GB**

4 Title of the invention — **COMPOUNDS**

5 Name of your agent *(if you know one)* — **RIE KONDO**

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

GLAXOSMITHKLINE
CORPORATE INTELLECTUAL PROPERTY
CN925.1
980 GREAT WEST ROAD
BRENTFORD
MIDDLESEX
TW8 9GS, GB

Patents ADP number *(if you know it)* 08471054001

6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of Filing (day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day / month / year)

8. Is a statement of inventorship and of right to grant a patent required in support of this request? *(Answer yes if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

YES

See note (d))

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	-
Description	50
Claim(s)	9
Abstract	-
Drawing(s)	-

10. If you are also filing any of the following, state how many against each item

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patent Form 9/77)*	
Request for substantive examination *(Patent Form 10/77)*	
Any other documents *(please specify)*	

11. **I/We request the grant of a patent on the basis of this application**

Signature RIE KONDO 21 November 2002
AGENT FOR THE APPLICANTS

12. Name and daytime telephone number of person to contact in the United Kingdom

JEAN HARNEY

020 8047 4420

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication of communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the patent Act 1977 stops you from applying for a patent abroad without first getting written permission form the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been received

a) Notes

If you need help to fill in this form or you have any questions, please contact the Patent Office on 0645 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form

If you have answered "Yes" Patents Form 7/77 will need to be filed.

d) Once you have filled in the form you must remember to sign and date it.

e) For details of the fee and ways to pay please contact the Patent Office.

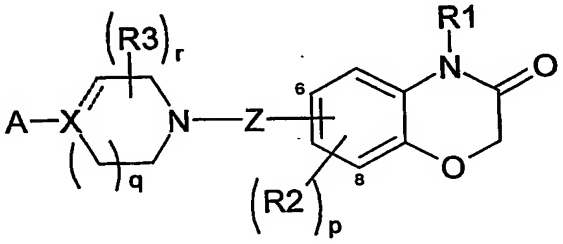
Compounds

The present invention relates to novel compounds, processes for their preparation, pharmaceutical compositions containing the same and their use as medicaments. More particularly this invention relates to novel benzoxazinone derivatives and their utility in the treatment of CNS and other disorders.

WO 97/45419 discloses a series of benzoxazinone compounds as dopamine D_4 receptor antagonists which are claimed to be useful in the treatment of psychosis and schizophrenia. EP 0900 792 A1 discloses a series of piperazine and piperidine derivatives as 5-HT_1 receptor agonists which are claimed to be useful for treating CNS disorders. WO02/34754 discloses a series of benzoxazinone compounds as being useful for treating certain CNS disorders such as depression. Patent application DT-2429253-A1 discloses certain benzoxazinone compounds including 2H-1,4-benzoxazin-3(4H)-one-6-[[4-(2-naphthalenyl)-1-piperazinyl]acetyl], 2H-1,4-benzoxazin-3(4H)-one-6-[[4-(1-naphthalenyl)-1-piperazinyl]acetyl], 2H-1,4-benzoxazin-3(4H)-one-6-[1-hydroxy-2-[4-(2-naphthalenyl)-1-piperazinyl]ethyl] 2H-1,4-benzoxazin-3(4H)-one-6-[1-hydroxy-2-[4-(1-naphthalenyl)-1-piperazinyl]ethyl] and salts thereof, which are claimed to be of sympatholytic, sedative, analgesic and anticholesteremic use.

Artigas (Trends in Pharmacological Sciences, Vol. 14, 262, 1993) suggests that the co-administration of a 5-HT_{1A} receptor antagonist and a selective serotonin reuptake inhibitor (SSRI) may give rise to an improvement in anti-depressant efficacy. Patent applications WO 00/40580 and WO 00/40581 both disclose a series of benzoxazine derivatives that are claimed to possess such a combined activity profile.

A novel series of benzoxazinone compounds has now been found that possess high affinity for 5-HT_1 type receptors and/or possess serotonin reuptake inhibition activity. The present invention therefore provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

A is a bicyclic 6,5 or 6,6 aromatic or heteroaromatic group which is optionally substituted by 1 - 4 substituents, which substituents may be the same or different,

and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, trifluoromethanesulfonyloxy, pentafluoroethyl, C_{1-6}alkoxy, arylC_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxyC_{1-6}alkyl, C_{3-7}cycloalkylC_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkylsulfonyl, arylsulfonyl, arylsulfonyloxy, C_{1-6}alkylsulfonamido, C_{1-6}alkylamido, Carylsulfonamido, arylcarboxamido, aroyl, arylC_{1-6}alkanoyl, and a group Ar^1-B, wherein B represents a single bond, O, S or CH_2 and Ar^1 represents a phenyl or a monocyclic heteroaromatic group, said Ar^1 group being optionally substituted by 1 - 3 substituents, which may be the same or different, and which are selected from the group consisting of a halogen, hydroxy, cyano, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkoxy or C_{1-6}alkanoyl;

R1 is hydrogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl or arylC_{1-6}alkyl;

R2 is independently halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy;

p is 0, 1 or 2;

R3 (a) is C_{1-6}alkyl and r is 0, 1, 2 or 3; or

(b) forms a bridge across the ring, the bridge consisting of a chain of 1 to 3 atoms, the bridge being optionally substituted by halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy; or

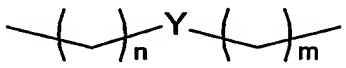
(c) is a chain of 1 to 3 atoms optionally substituted by halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy, the chain being attached to an available carbon atom in Z;

X is CH, N or C;

⋯⋯ represents a single bond when X is CH or N; and ═══ represents a double bond when X is C;

q is 1 or 2; and

Z is attached to the 6-position or the 8-position of the benzoxazinone group and is a 3 to 7 membered cycloalkylene group , 3 to 7 membered cycloalkenylene group, -(CH=CH)- or a group



wherein m and n are independently 0, 1 or 2, and Y is a single bond, 3 to 7 membered cycloalkylene group, 3 to 7 membered cycloalkenylene group, -(CH=CH)-, -C(=O)-, -C(=CH_2)-, oxygen, or a methylene group optionally substituted by one or two groups selected from halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy;

provided that when A is naphthyl, 5,6,7,8-tetrahydronaphthyl or 2,3-dihydoindene, Z is not -(CH_2CH(OH))- , -(CH_2CH_2CH(OH))- or -(CH_2C(=O) .

Where used herein the term naphthyl, whether alone or as part of another group, is intended, unless otherwise stated, to denote both 1-naphthyl and 2-naphthyl groups.

The term "bicyclic 6,5 or 6,6 aromatic or heteroaromatic group" refers to stable bicyclic aromatic groups having 9 or 10 carbon atoms in total, as well as stable bicyclic heteroaromatic groups having 9 or 10 atoms in total and containing 1 to 4 heteroatoms selected from oxygen, nitrogen and sulphur. Examples of bicyclic 6,5 or 6,6 aromatic groups include naphthyl, 5,6,7,8-tetrahydronaphthyl and 2, 3-dihydoindene. Examples of bicyclic 6,5 or 6,6 heteroaromatic groups include indolyl, quinolyl, quinazolinyl, 2,3-dihydrobenzodioxinyl, isoquinolyl, benzofuranyl, benzothienyl, benzimidazolyl, indazolyl, 4-, 5-, 6- or 7-azaindolyl, benzothiazolyl, benzoxazolyl, benzisoxazolyl, benzisothiazolyl, quinoxalinyl and cinnolinyl.

The term "monocyclic heteroaromatic group" refers to stable monocyclic heteroaromatic groups having 5 or 6 atoms in total and containing 1 to 4heteroatoms selected from oxygen, nitrogen and sulphur. Examples of monocyclicheteroaromatic groups include pyrrolyl, pyrrolinyl, pyrazolinyl, imidazolyl, pyrazolyl, oxadiazolyl, isothiazolyl, thiazolyl, thiazinyl, furyl, thienyl, pyridyl, pyridazinyl, pyrimidinyl and pyrazinyl.

The term "aryl", whether alone or as part of another group, is intended, unless otherwise stated, to denote an aromatic carbocyclic or heterocyclic group such as phenyl, pyrrolyl, pyrrolinyl, pyrazolinyl, imidazolyl, pyrazolyl, oxadiazolyl, isothiazolyl, thiazolyl, thiazinyl, furyl, thienyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl, azepinyl or naphthyl, optionally substituted by one or more halogen, C_{1-6}alkyl, CF_3, cyano, hydroxy, C_{1-6}alkanoyl, or C_{1-6}alkoxy.

The term "C_{1-6}alkyl", whether alone or part of another group, refers to alkyl groups having from one to six carbon atoms, in all isomeric forms, including methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, sec-pentyl, n-pentyl, isopentyl, tert-pentyl and hexyl.

The term "halogen" is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine and iodine.

The term "haloC_{1-6}alkyl" refers to C_{1-6}alkyl groups with one or more halo substituents, for example CF_3.

The term "C_{1-6}alkanoyl" refers to an alkanoyl group having from 1 to 6 carbon atoms, such as methanoyl (or "formyl"), ethanoyl (or "acetyl"), propanoyl, butanoyl, pentanoyl and hexanoyl.

The term "C_{1-6}alkoxy" refers to a straight chain or branched chain alkoxy (or "alkyloxy") group having from one to six carbon atoms, such as methoxy, ethoxy,

propoxy, isopropoxy, butoxy, isobutoxy, sec-butoxy, tert-butoxy, pentoxy, neopentoxy, sec-pentoxy, n-pentoxy, isopentoxy, tert-pentoxy and hexoxy.

The term "3 to 7 membered cycloalkylene group" refers to cycloalkylene groups having from 3 to 7 carbons, such as cyclohexylene.

The term "3 to 7 membered cycloalkenylene group" refers to cycloalkenylene groups having from 3 to 7 carbons, such as cyclohexenylene.

The term "C_{1-6}alkylthio" refers to a straight chain or branched chain alkylthio group having from one to six carbon atoms, such as methylthio, ethylthio, propylthio, isopropylthio, butylthio, isobutylthio, sec-butylthio, tert-butylthio, pentylthio, neopentylthio, sec-pentylthio, n-pentylthio, isopentylthio, tert-pentylthio and hexylthio.

The term "arylC_{1-6}alkoxy" refers to an aryl group which is linked by a C_{1-6}alkoxy group. Examples include phenylmethoxy, phenylethoxy, naphthymethoxy, naphthylethoxy, phenylpropoxy, naphthylpropoxy, phenylbutoxy and naphthylpentoxy.

The term "C_{3-7}cycloalkyl" refers to a cycloalkyl group consisting of from 3 to 7 carbon atoms, for example cyclopropane, cyclobutane, cyclopentane, cyclohexane and cycloheptane.

The term "aroyl" refers to a group having the formula "aryl-CO" wherein "aryl" is as defined above.

The term "C_{3-6}alkenyl" refers to an unsaturated hydrocarbon group containing one or more C=C bonds and having from three to six carbon atoms, in all isomeric forms, such as propenyl, butenyl, pentenyl, and hexenyl.

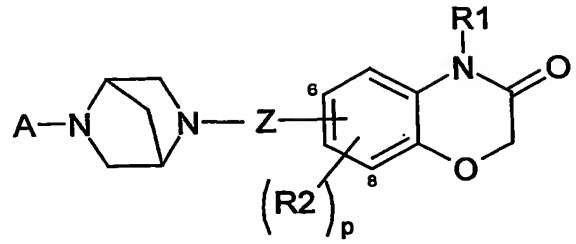
The term "C_{3-6}alkynyl" refers to an unsaturated hydrocarbon group containing one or more triple C-C bonds, having from three to six carbon atoms, in all isomeric forms, such as propynyl, butylidyne, pentenynyl, and pentylidyne.

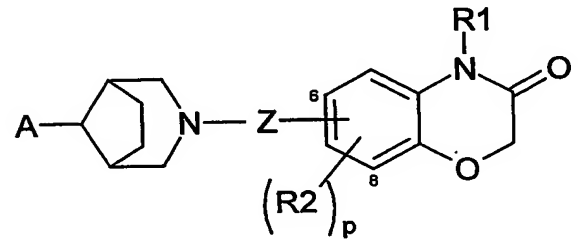
When R1 is C_{1-6}alkyl, a preferred group is methyl or ethyl. Preferably R1 is hydrogen or methyl.

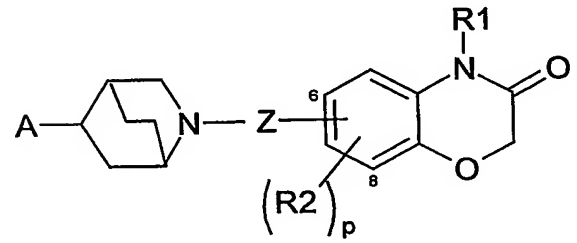
When p is other than 0, preferably R2 is halogen (particularly fluoro or chloro) or C_{1-6}alkyl (particularly methyl or ethyl).

R3 may be a chain of 1 to 3 atoms optionally substituted by halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy. Suitably, the chain of atoms consists of 1 to 3 atoms selected from carbon, oxygen, nitrogen and sulfur.

Examples of groups formed when R3 is a chain of 1 to 3 atoms forming a bridge across the ring are:

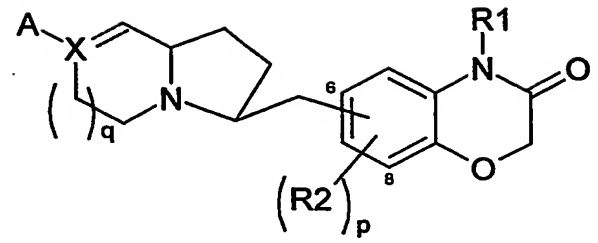


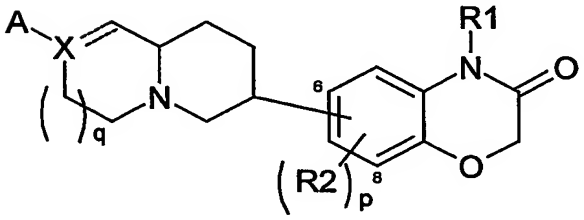




Alternatively, R3 maybe a chain of 1 to 3 atoms optionally substituted by halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy, wherein the chain is attached to an available carbon atom in group Z. Suitably, the chain of atoms consists of 1 to 3 atoms selected from carbon, oxygen, nitrogen and sulfur.

Examples of compounds wherein R3 forms a chain of atoms attached to an available carbon atom in group Z include:





Preferably R3 is methyl.

Preferably X is CH or N and ------ is a single bond.

Preferably q is 1.

When Z is a 3 to 7 membered cycloalkenylene group, preferably it is cyclohexenylene. Preferably Z is $-(CH_2)_2-$.

If A is a bicyclic 6,5 or 6,6 aromatic group, preferably A is 5,6,7,8-tetrahydronapthalenyl, optionally substituted as defined above. Preferably A is a bicyclic 6,5 or 6,6 heteroaromatic group which is optionally substituted by 1 - 4 substituents as defined above.

Preferably A is indolyl, quinolyl, quinazolinyl or 2,3-dihydrobenzodioxinyl, said groups being optionally substituted as defined below.

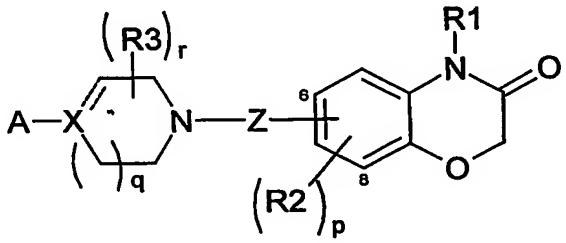
When a substituent on A is a further group Ar^1-B, Ar^1 is preferably a monocyclic heteroaromatic group (particularly isoxazolyl or oxadiazolyl), optionally substituted as defined above. Preferably B is a single bond.

Preferred optional substituents for A are halogen (particularly fluoro or chloro), C_{1-6}alkyl (particularly methyl, ethyl and propyl), cyano, CF_3, C_{1-6}alkoxy (particularly methoxy, ethoxy or isopropoxy), C_{1-6}alkanoyl or a group Ar^1-B as defined above.

Most particularly preferred A groups, including optional substituents, are 5-quinolyl(2-Me), 5-quinolyl(2-Me, 7-Cl), 5-quinolyl(2-Me, 7-F) and 5-quinazolinyl(2-Me), 5-

quinolyl(2-Me, 7-Me), 5-dihydrobenzo[1,4]dioxinyl, 8-quinolyl(6-methoxy), 8-quinolyl, 4-indolyl and 4-indolyl (2-Me).

Thus, in a further aspect the present invention provides a compound of formula (Ia) or a pharmaceutically acceptable salt thereof:



(Ia)

wherein:

A is a bicyclic 6,5 or 6,6 heteroaromatic group which is optionally substituted by 1 - 4 substituents, which substituents may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, trifluoromethanesulfonyloxy, pentafluoroethyl, C_{1-6}alkoxy, arylC_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxyC_{1-6}alkyl, C_{3-7}cycloalkylC_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkylsulfonyl, arylsulfonyl, arylsulfonyloxy, C_{1-6}alkylsulfonamido, C_{1-6}alkylamido, Arylsulfonamido, arylcarboxamido, aroyl, arylC_{1-6}alkanoyl, and a group Ar^1-B, wherein B represents a single bond, O, S or CH_2 and Ar^1 represents a phenyl or a monocyclic heteroaromatic group, said Ar^1 group being optionally substituted by 1 - 3 substituents, which may be the same or different, and which are selected from the group consisting of a halogen, hydroxy, cyano, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkoxy or C_{1-6}alkanoyl;

R1 is hydrogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl or arylC_{1-6}alkyl;

R2 is independently halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy;

p is 0, 1 or 2;

R3 (a) is C_{1-6}alkyl and r is 0, 1, 2 or 3; or

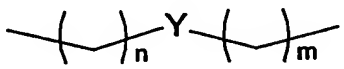
(b) forms a bridge across the ring, the bridge consisting of a chain of 1 to 3 atoms, the bridge being optionally substituted by halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy; or

(c) is a chain of 1 to 3 atoms optionally substituted by halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy, the chain being attached to an available carbon atom in Z;

X is CH, N or C;

------ represents a single bond when X is CH or N; and ====== represents a double bond when X is C;

q is 1 or 2; and
Z is attached to the 6-position or the 8-position of the benzoxazinone group and is a 3 to 7 membered cycloalkylene group , 3 to 7 membered cycloalkenylene group, -(CH=CH)- or a group



wherein m and n are independently 0, 1 or 2, and Y is a single bond, 3 to 7 membered cycloalkylene group, 3 to 7 membered cycloalkenylene group, -(CH=CH)-, -C(=O)-, -C(=CH_2)-, oxygen, or a methylene group optionally substituted by one or two groups selected from halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy.

Preferred features of formula (I) apply to formula (Ia) *mutatis mutandis*.

Preferred compounds of this invention are:
6-{2-[4-(2-Methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt
6-{2-[4-(2,7-Dimethylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloride salt
6-{2-[4-(7-Chloro-2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloride salt
6-[2-(4-Quinolin-4-ylpiperazin-1-yl)ethyl]-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt
6-{2-[4-(2-Methylquinazolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt
6-{2-[4-(2,3-Dihydrobenzo[1,4]dioxin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt
6-{2-[4-(6-Methoxyquinolin-8-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt
6-[2-(4-Quinolin-8-yl)piperazin-1-yl)ethyl]-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt
6-{2-[4-(1*H*-Indol-4-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt
6-{2-[4-(7-Chloro-2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-7-fluoro-4*H*-benzo[1,4]oxazin-3-one
4-Methyl-6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt
6-{2-[4-(2-Methylquinolin-5-yl)piperazin-1-yl]ethanoyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt
6-{1-Hydroxy-2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt

6-{2-[4-(2-Methyl-4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt

6-{2-[3-Methyl-4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt

6-{2-[2-Methyl-4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt

6-{2-[4-(2-Methylquinolin-5-yl)-3,6-dihydro-2*H*-pyridin-1-yl]ethyl}-4H-benzo[1,4]oxazin-3-one

6-{2-[4-(2-Methylquinolin-5-yl)piperidin-1-yl]ethyl}-4-H-benzo[1,4]oxazin-3-one hydrochloride salt

6-{2-[4-(2-Methylquinolin-5-yl)-[1,4]diazepan-1-yl]ethyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloride salt

6-{2-[4-(2-Methylquinazolin-5-yl)-[1,4]diazepan-1-yl]ethyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloride salt

7-Fluoro-6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt

6-{3-[4-(2-Methylquinolin-5-yl)-piperazin-1-yl]-propyl}-4*H*-benzo[1,4]-oxa-zin-3-one acetic acid salt

6-{3-[4-(7-Fluoro-2-methylquinolin-5-yl)piperazin-1-yl]-propyl}-4*H*-benzo-[1,4]oxazin-3-one

6-{3-[4-(2-Methylquinolin-5-yl)-piperazin-1-yl]-propanoyl}-4*H*-benzo[1,4]-oxa-zin-3-one hydrochloric acid salt

6-{1-Hydroxy-3-[4-(2-methylquinolin-5-yl)-piperazin-1-yl]-propyl}-4*H*-benzo-[1,4]oxazin-3-one hydrochloric acid salt

6-{(E)-3-[4-(2-Methylquinolin-5-yl)piperazin-1-yl]propenyl}-4*H*-benzo[1,4]-oxa-zin-3-one hydrochloric acid salt

6-{4-[4-(2-Methylquinolin-5-yl)piperazin-1-yl]butyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloric acid salt

6-{4-[4-(2-Methylquinolin-5-yl)piperazin-1-yl]-cyclohex-1-enyl}-4*H*-benzo[1,4]-oxazin-3-one hydrochloric acid salt

6-{4-[4-(2-Methylquinazolin-5-yl)piperazin-1-yl]butyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloric acid salt

6-{2-[4-(2-Methylquinolin-5-yl)piperazin-1-yl]ethoxy}-4-H-benzo[1,4]oxazin-3-one

4-Methyl-6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethoxy}-4-H-benzo[1,4]oxazin-3-one

7-Fluoro-6-{2-[4-(7-fluoro-2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloride salt

6-{2-[4-(7-fluoro-2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloride salt

7-Fluoro-6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethanoyl}-4*H*-benzo[1,4]oxazin-3-one

6-{1-Hydroxy-2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]-oxazin-3-one

6-{1-Methoxy-3-[4-(2-methylquinolin-5-yl)piperazin-1-yl]propyl}-4*H*-benzo[1,4]-oxazin-3-one
6-{2-[4-(2-Methyl-1*H*-indol-4-yl)piperazin-1-yl]-ethyl}-4*H*-benzo-[1,4]oxazin-3-one hydrochloric acid salt
6-{2-[4-(5,6,7,8-Tetrahydronaphthalen-1-yl)piperazin-1-yl]ethyl}-4*H*-benzo-[1,4]oxazin-3-one
6-[2-(4-Naphthalen-1-ylpierazin-1-yl)ethyl]-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt
6-{1-Fluoro-2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]-oxazin-3-one
6-{1-Fluoro-3-[4-(2-methylquinolin-5-yl)piperazin-1-yl]propyl}-4*H*-benzo[1,4]-oxazin-3-one
5-Fluoro-6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]-oxazin-3-one
5-Fluoro-4-methyl-6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]-oxazin-3-one
6-{2-[4-(7-Chloro-2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4-methyl-4*H*-benzo-[1,4]-oxazin-3-one
4-Ethyl-6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]-oxazin-3-one hydrochloride salt
6-{2-[4-(7-Fluoro-2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4-methyl-4*H*-benzo-[1,4]-oxazin-3-one hydrochloride salt
and pharmaceutically acceptable salts thereof.

The compounds of formula (I) can form acid addition salts thereof. It will be appreciated that for use in medicine the salts of the compounds of formula (I) should be pharmaceutically acceptable. Suitable pharmaceutically acceptable salts will be apparent to those skilled in the art and include those described in *J. Pharm. Sci.*, 1977, 66, 1-19, such as acid addition salts formed with inorganic acids e.g. hydrochloric, hydrobromic, sulfuric, nitric or phosphoric acid; and organic acids e.g. succinic, maleic, acetic, fumaric, citric, tartaric, benzoic, p-toluenesulfonic, methanesulfonic or naphthalenesulfonic acid. Certain of the compounds of formula (I) may form acid addition salts with one or more equivalents of the acid. The present invention includes within its scope all possible stoichiometric and non-stoichiometric forms.

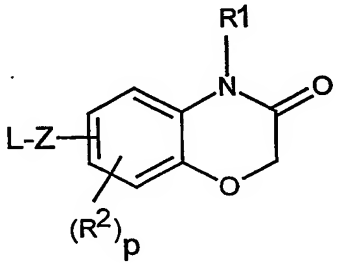
The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and, if crystalline, may optionally be hydrated or solvated. This invention includes within its scope stoichiometric hydrates or solvates as well as compounds containing variable amounts of water and/or solvent.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms (e.g. geometric or ("*cis-trans*") isomers, diastereomers and enantiomers) and the

invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis. The invention also extends to any tautomeric forms and mixtures thereof. For compounds of formula (I) where R^1 is a C_{3-6}alkenyl group, the compounds may also exist as geometric isomers around the double bond. The present invention includes within its scope all such isomers, including mixtures.

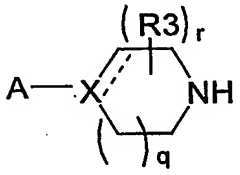
In a further aspect, this invention provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

(a) reacting a compound of formula (II):



(II)

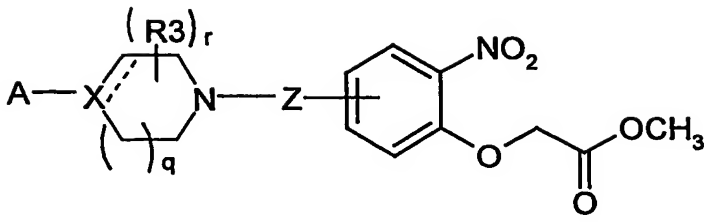
wherein R1, R2, p and Z are as defined in formula (I), and L is a leaving group, with a compound of formula (III):



(III)

wherein A, R3, ---, X, r and q are as defined in formula (I); or

(b) the reduction and concominant cyclisation of a compound of formula (IV):



(IV)

in which A, X, R3, ---, q, r and Z are as defined in formula (I);

and optionally thereafter for each of process (a) or (b):

- removing any protecting groups, and/or
- converting a compound of formula (I) into another compound of formula (I), and/or
- forming a pharmaceutically acceptable salt.

For process (a), the reaction of a compound of formula (II) and (III) is carried out in the presence of a base such as sodium carbonate or potassium carbonate, in the presence of sodium iodide in a suitable solvent, such as NMP or MIBK at an elevated temperature.

For process (b), the reduction and concominant cyclisation of a compound of formula (IV) is carried out in the presence of a reducing agent such as iron powder in glacial acetic acid.

Compounds of formula (I) can be converted into further compounds of formula (I) using standard techniques. For example, and by way of illustration rather than limitation, for compounds of formula (I) wherein R1 is hydrogen it may be possible to introduce a C_{1-6}alkyl group by conventional alkylation using 1 molar equivalent of a C_{1-6}alkylhalide and 1 molar equivalent of a suitable base in an inert solvent.

Compounds of formulae (II)-(IV) are commercially available, may be prepared according to procedures described herein, by known literature methods, or by analogous procedures thereto.

It will be appreciated by those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above procedures. Standard protection and deprotection techniques, such as those described in Greene T.W. *Protective groups in organic synthesis*, New York, Wiley (1981), can be used. For example, primary amines can be protected as phthalimide, benzyl, t-butyloxycarbonyl, benzyloxycarbonyl or trityl derivatives. Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection of such groups is achieved using

conventional procedures well known in the art. For example, protecting groups such as t-butyloxycarbonyl may be removed using an acid such as hydrochloric or trifluroroacetic acid in a suitable solvent such as dichloromethane, diethylether, isopropanol or mixtures thereof.

It will be further appreciated that compounds of formula (II)-(IV) and any precursors thereto may have one or more chiral centres. Enantiomeric or diastereomeric mixtures of such compounds may be separated using conventional methods, for example by chromatography or by resolution by means of diastereomeric salt formation.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I), or formula (Ia) as defined above and a pharmaceutically acceptable carrier or excipient.

In a further aspect, the present invention provides a process for preparing a pharmaceutical composition, the process comprising mixing a compound of formula (I) or formula (Ia) as defined above and a pharmaceutically acceptable carrier or excipient.

The affinities of the compounds of this invention for 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors can be determined by the following assay. CHO cells expressing 5-HT_{1A} receptors (4×10^7 cells/ml) are homogenised in Tris buffer and stored in 1ml aliquots. CHO cells expressing 5-HT_{1B} receptors (4×10^7 cells/ml) are homogenised in Tris buffer and stored in 1.5 ml aliquots. CHO cells expressing 5-HT_{1D} receptors (1×10^8/ml) are homogenised in Tris buffer and stored in 1 ml aliquots. 0.4 ml of a cell suspension is incubated with [^{3}H]-5-HT (4nM) for 5-$HT_{1B/1D}$ receptors and [^{3}H]WAY100635 (1nM) for 5-HT_{1A} receptors in Tris Mg HCl buffer (pH 7.7) and test drug, at 37^{o}C for 45 minutes. Each test drug is tested at 10 concentrations (0.01 mM to 0.3 nM final concentration), with non-specific binding defined using 0.01 mM 5-HT. The total assay volume is 0.5 ml. Incubation is stopped by rapid filtration using a Packard Filtermate and radioactivity measured by Topcount scintillation counting. pKi values are calculated from the IC_{50} generated by an iterative least squares curve fitting programme.

All the Example compounds shown below were tested according to the radioligand binding assay described above and were found to have pKi values > 6.0 at 5-HT_{1A} receptors, with many showing a considerably higher affinity (having pKi values in the range 8.0 – 10.0) Certain compounds of this invention also demonstrate comparable affinity for 5-HT_{1B} and 5-HT_{1D} receptors.

The intrinsic activity of the compounds of this invention can be determined according to the following assay. HEK293 cell membranes stably expressing human 5-HT_{1A} receptors and CHO cell membranes stably expressing human 5-HT_{1B} receptors are homogenised in HEPES/EDTA buffer and stored in 1ml aliquots, and [^{35}S]GTPγS binding studies are carried out essentially as described by Lazareno *et al.*, (Life Sci., 1993, **52**, 449) with some minor modifications. Membranes from 10^6 cells are pre-incubated at 30°C for 30 minutes in 20 mM HEPES buffer (pH 7.4) in the presence of $MgCl_2$ (3 mM), NaCl (100 mM), GDP (10 μM) and ascorbate (0.2 mM), with or without test compounds. The reaction is started by the addition of 50 μl of [^{35}S]GTPγS (100 pM, assay concentration) followed by a further 30 minutes incubation at 30°C. Non-specific binding is determined using nonradiolabelled GTPγS (20 μM) added prior to the membranes. The reaction is terminated by rapid filtration through Whatman GF/B grade filters followed by 5 x 1 ml washes with ice cold HEPES (20 mM) /$MgCl_2$ (3 mM) buffer. Radioactivity is measured using liquid scintillation spectrometry. This procedure is hereafter referred to as the [^{35}S]GTPγS functional assay.

It has been found, using the [^{35}S]GTPγS functional assay, that certain compounds of formula (I) appear to be antagonists at 5-HT_1 type receptors whilst others appear to be inverse agonists, agonists or partial agonists.

The efficacy of the compounds of this invention to inhibit the re-uptake ofserotonin can be measured in a 5-HT uptake assay by measurement of uptake of [^{3}H]-5-HT into LLCPK cells expressing human or rat serotonin transporters. In brief, cells are harvested and plated onto 96-well plates (10,000 cells per well). 24hr later cells are washed 2x with HBSSH (Hanks'balanced salt solution + 20mM HEPES). 50ul of test compound or vehicle is added to each well and incubated for 10min. Subsequently, [^{3}H]5-HT (final concentration 25nM) is added and the test mixture is incubated for a further 7min. The reaction is terminated by aspiration of test mixture and the cells are washed 6x with HBSSH. 50ul of scintillation cocktail (Microscint-20, Packard) is added onto the cells and the top and bottom of the plate is sealed. Plates areread, 30min later, in a Packard TopCount.

Some of the Example compounds tested according to this uptake assay were found to have potency at the uptake site of pIC_{50} of > 6.0. Some showed a considerably higher potency (pIC_{50} > 7.0).

Certain compounds of formula (I) , formula (Ia) and formula (Ib) as defined above demonstrate both affinity for the 5-HT_{1A} receptor (or affinity for 5-HT_{1A}, 5-HT_{1B} and 5-HT_{1D} receptors) and potency at the 5-HT uptake site in the higher ranges indicated above.

Compounds of the present invention are of use in the treatment of certain CNS disorders, particularly serotonin-related disorders such as depression (which term is used herein to include bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, seasonal affective disorder, dysthymic disorders with early or late onset and with or without atypical features, neurotic depression and social phobia, depression accompanying dementia for example of the Alzheimer's type, vascular dementia with depressed mood, schizoaffective disorder or the depressed type, and depressive disorders resulting from general medical conditions including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, *etc*), anxiety disorders (including generalised anxiety disorder and social anxiety disorder), schizophrenia, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder, pain (particularly neuropathic pain), memory disorders, including dementia, amnesic disorders and age-associated memory impairment, disorders of eating behaviours, including anorexia nervosa and bulimia nervosa, sexual dysfunction, sleep disorders (including disturbances of circadian rhythm, dyssomnia, insomnia, sleep apnea and narcolepsy), withdrawal from abuse of drugs such as of cocaine, ethanol, nicotine, benzodiazepines, alcohol, caffeine, phencyclidine (phencyclidine-like compounds), opiates (e.g. cannabis, heroin, morphine), amphetamine or amphetamine-related drugs (e.g. dextroamphetamine, methylamphetamine) or a combination thereof, motor disorders such as Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders.

Compounds of the present invention may also have utility in the treatment of certain gastrointestinal disorders such as irritable bowel syndrome, Crohn's disease, ulcerative colitis, non-steroidal anti-inflammatory drug induced damage.

It is to be understood that the term "treatment" as used herein includes amelioration of established symptoms as well as prevention.

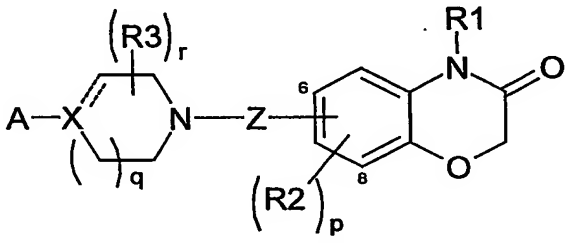
Thus, the present invention provides a compound of formula (I) or formula (Ia) as defined above or a pharmaceutically acceptable salt thereof for use in therapy.

In order to use the compounds of the present invention in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or formula (Ia) as defined above or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

In a further aspect, the present invention provides a process for preparing a pharmaceutical composition, the process comprising mixing a compound of formula (I) or formula (Ia) as defined above or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

As indicated above, DT-2429253-A1 discloses certain benzoxazinone compounds. However, these compounds have not previously been disclosed to have utility in the treatment of serotonin-related disorders.

Accordingly, the present invention provides a compound of formula (Ib) or a pharmaceutically acceptable salt thereof:



(Ib)

wherein:

A is a bicyclic 6,5 or 6,6 aromatic or heteroaromatic group which is optionally substituted by 1 - 4 substituents, which substituents may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, trifluoromethanesulfonyloxy, pentafluoroethyl, C_{1-6}alkoxy, arylC_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxyC_{1-6}alkyl, C_{3-7}cycloalkylC_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkylsulfonyl, arylsulfonyl, arylsulfonyloxy, C_{1-6}alkylsulfonamido, C_{1-6}alkylamido, Arylsulfonamido, arylcarboxamido, aroyl, arylC_{1-6}alkanoyl, and a group Ar^1-B, wherein B represents a single bond, O, S or CH_2 and Ar^1 represents a phenyl or a monocyclic heteroaromatic group, said Ar^1 group being optionally substituted by 1 - 3 substituents, which may be the same or different, and which are selected from the group consisting of a halogen, hydroxy, cyano, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkoxy or C_{1-6}alkanoyl;

R1 is hydrogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl or arylC_{1-6}alkyl;

R2 is independently halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy;

p is 0, 1 or 2;

R3 (a) is C_{1-6}alkyl and r is 0, 1, 2 or 3; or

(b) forms a bridge across the ring, the bridge consisting of a chain of 1 to 3 atoms, the bridge being optionally substituted by halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy; or

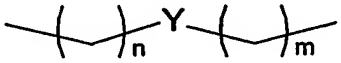
(c) is a chain of 1 to 3 atoms optionally substituted by halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy, the chain being attached to an available carbon atom in Z;

X is CH, N or C;

⎓ represents a single bond when X is CH or N; and ⎓ represents a double bond when X is C;

q is 1 or 2; and

Z is attached to the 6-position or the 8-position of the benzoxazinone group and is a 3 to 7 membered cycloalkylene group , 3 to 7 membered cycloalkenylene group, -(CH=CH)- or a group



wherein m and n are independently 0, 1 or 2, and Y is a single bond, 3 to 7 membered cycloalkylene group, 3 to 7 membered cycloalkenylene group, -(CH=CH)-, -C(=O)-, -C(=CH_2)-, oxygen, or a methylene group optionally substituted by one or two groups selected from halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy;

for use in the treatment of a serotonin-related disorder.

The serotonin-related disorder may be depression (which term is used herein to include bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, seasonal affective disorder, dysthymic disorders with early or late onset and with or without atypical features, neurotic depression and social phobia, depression accompanying dementia for example of the Alzheimer's type, vascular dementia with depressed mood, schizoaffective disorder or the depressed type, and depressive disorders resulting from general medical conditions including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion, *etc*), anxiety disorders (including generalised anxiety disorder and social anxiety disorder), schizophrenia, panic disorder, agoraphobia, social phobia, obsessive compulsive disorder and post-traumatic stress disorder, pain (particularly neuropathic pain), memory disorders, including dementia, amnesic disorders and age-associated memory impairment, disorders of eating behaviours, including anorexia nervosa and bulimia nervosa, sexual dysfunction, sleep disorders (including disturbances of circadian rhythm, dyssomnia, insomnia, sleep apnea and narcolepsy), withdrawal from abuse of drugs such as of cocaine, ethanol, nicotine, benzodiazepines, alcohol, caffeine, phencyclidine (phencyclidine-like compounds), opiates (e.g. cannabis, heroin, morphine), amphetamine or amphetamine-related drugs (e.g. dextroamphetamine, methylamphetamine) or a combination thereof, motor disorders such as Parkinson's disease, dementia in Parkinson's disease, neuroleptic-induced Parkinsonism and tardive dyskinesias, as well as other psychiatric disorders.

Preferably the disorder is depression or anxiety.

All preferred features of formula (I) and (Ia) apply to compounds of formula (Ib) *mutatis mutandis.*

The present invention also provides use of a compound of formula (Ib) or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a serotonin-related disorder for example as defined above. Preferably the disorder is depression or anxiety.

Furthermore, the present invention provides a method of treatment of a serotonin-related disorder for example as defined above, comprising administering to a mammal in need thereof a safe and effective amount of a compound of formula (Ib) or a pharmaceutically acceptable salt thereof. Preferably the disorder is depression or anxiety.

Compounds of the present invention may be administered in combination with other active substances such as 5HT3 antagonists, NK-1 antagonists, serotonin agonists, selective serotonin reuptake inhibitors (SSRI), noradrenaline re-uptake inhibitors (SNRI), tricyclic antidepressants and/or dopaminergic antidepressants.

Suitable 5HT3 antagonists which may be used in combination of the compounds of the inventions include for example ondansetron, granisetron, metoclopramide.

Suitable serotonin agonists which may be used in combination with the compounds of the invention include sumatriptan, rauwolscine, yohimbine, metoclopramide.

Suitable SSRIs which may be used in combination with the compounds of the invention include fluoxetine, citalopram, femoxetine, fluvoxamine, paroxetine, indalpine, sertraline, zimeldine.

Suitable SNRIs which may be used in combination with the compounds of the invention include venlafaxine and reboxetine.

Suitable tricyclic antidepressants which may be used in combination with a compound of the invention include imipramine, amitriptiline, chlomipramine and nortriptiline.

Suitable dopaminergic antidepressants which may be used in combination with a compound of the invention include bupropion and amineptine.

It will be appreciated that the compounds of the combination or composition may be administered simultaneously (either in the same or different pharmaceutical formulations), separately or sequentially.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose);, fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate);, tabletting lubricants lubricants (e.g. magnesium stearate, talc or silica);, disintegrants (e.g. potato starch or sodium starch glycollate); and acceptable wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats), emulsifying agents (e.g. lecithin or acacia), non-aqueous vehicles (which may include edible oils e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils), preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid), and, if desired, conventional flavourings or colorants, buffer salts and sweetening agents as appropriate. Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose, utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle, optionally with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the

compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents. Drops may be formulated with an aqueous or non-aqueous base also comprising one or more dispersing agents, stabilising agents, solubilising agents or suspending agents. They may also contain a preservative.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

For intranasal administration, the compounds of the invention may be formulated as solutions for administration via a suitable metered or unitary dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device. Thus compounds of formula (I) may be formulated for oral, buccal, parenteral, topical (including ophthalmic and nasal), depot or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be

0.05 to 1000 mg, more suitably 1.0 to 200 mg, and such unit doses may be administered more than once a day, for example two or three times a day. Such therapy may extend for a number of weeks or months.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Descriptions and Examples illustrate the preparation of the compounds of the invention.

Description 1

2-Methylquinolin-5-yl trifluoromethanesulfonate (D1)

A solution of 2-methylquinolin-5-ol (2.5 g; 15.7 mmol) (WO/0234754) in dry DCM (25 mL) and pyridine (6.4 mL; 5 eq.) was cooled to 0°C and trifluoromethanesulfonic anhydride (4.2 mL; 1.6 eq) was added dropwise over 10 minutes. The reaction mixture was stirred under nitrogen at r.t. for 1 h, then poured into water (20 mL) and extracted into ethyl acetate (3x15 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography, eluting with 40% ethyl acetate in cyclohexane to afford the title compound (**D1**) as a yellow solid (4.2 g; yield 92%).

MS; (ES) m/z: 292.3 [MH^+]. $C_{11}H_8F_3NO_3S$ requires 291.

1H-NMR (300 MHz, DMSO) δ: 8.05 (d, 1 H), 7.85 (d, 1 H), 7.64 (t, 1H), 7.48 (d, 1 H), 7.43 (d, 1 H), 2.48 (s, 3 H).

Description 2

***tert*-Butyl 4-(2-methylquinolin-5-yl)piperazine-1-carboxylate (D2)**

tert-Butyl 1-piperazinecarboxylate (3.8 g; 1.2 eq.), caesium carbonate (8.4 g; 1.5 eq.), palladium acetate (0.31 g; 0.08 eq.) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (1.3 g; 0.12 eq.) were added to a solution of 2-methyl-quinolin-5-yl-trifluoro-methanesulfonate (**D1**) (5.0 g, 0.017 mol) in dry toluene (150 mL) under nitrogen. The reaction mixture was stirred at reflux under nitrogen for 8 h. The reaction was then cooled to r.t. and quenched with a saturated aqueous solution of ammonium chloride (100 mL) and then extracted with ethyl acetate (3x100 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography, eluting with 30% ethyl acetate in cyclohexane to afford the title compound (**D2**) as a yellow oil (4.74 g; yield 84%).

MS; (ES) m/z: 328.4 [$MH]^+$. $C_{19}H_{25}N_3O_2$ requires 327.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.40 (d, 1 H), 7.76 (d, 1 H), 7.61 (t, 1 H), 7.29 (d, 1 H), 7.06 (d, 1 H), 3.69 (bs, 4 H), 3.03 (bs, 4 H), 2.74 (s, 3 H), 1.51 (s, 9 H).

Description 3

2-Methyl-5-piperazin-1-ylquinoline (D3)

tert-Butyl 4-(2-methyl-quinolin-5-yl)piperazine-1-carboxylate (**D2**) (1.1 g, 3.9 mmol) in a 25% solution of trifluoroacetic acid in DCM (10 mL) was stirred at r.t. under nitrogen for 3 h. The reaction mixture was concentrated *in vacuo* and filtered through a 20g SCX cartridge to afford the title compound (**D3**) as a yellow solid (0.74 g; yield 96%).

MS; (ES) m/z: 228.4 $[MH]^+$. $C_{14}H_{17}N_3$ requires 227.

^{1}H-NMR (300 MHz, DMSO) δ: 8.34 (d, 1 H), 7.57 (m, 2 H), 7.35 (m, 1 H), 7.06 (m, 1 H), 2.93 (bm, 8 H), 2.62 (s, 3 H).

Description 4

6-(2-Chloroethyl)-4*H*-benzo[1,4]oxazin-3-one (D4)

A solution of 6-(2-chloroethanoyl)-2*H*-benz[1,4]oxazin-3-one (5.0 g, 22.16 mmol) in trifluoroacetic acid (30 mL) was cooled to 0°C and triethylsilane (7.8 mL; 2.3 eq) was added dropwise over 2 minutes. The reaction mixture was stirred under nitrogen at 0°C for 10 minutes, warmed to 45°C for 20 minutes and then allowed to stir at r.t. overnight. It was then poured into ice/ saturated aqueous sodium bicarbonate (20 mL) and extracted into ethyl acetate (3x15 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was washed with hexane (30 mL), stirred vigorously for 3h, filtered and dried (Na_2SO_4) to give the title compound (**D4**) as a white solid (4.3 g; yield 91%).

MS; (ES) m/z: 212.1 $[MH]^+$. $C_{10}H_{10}ClNO_2$ requires 211.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.10 (bs, 1 H), 6.88 (d, 1 H), 6.82 (dd, 1 H), 6.65 (d, 1 H), 4.57 (s, 2 H), 3.65 (t, 2 H), 2.98 (t, 2 H).

Description 5

2,7-Dimethyl-5,6,7,8-tetrahydroquinoline-5-one (D5)

A solution of 3-amino-5-methylcyclohex-2-enone (5 g; 40 mmol) in 4-methoxy-3-buten-2-one (7 mL) was heated under nitrogen from 100 to 160°C over 0.5 h, then at 170°C for 2 h using a Dean Stark set up. The crude reaction mixture was purified by SPE-SI bond elute, eluting with 20% ethyl acetate in cyclohexane to afford the title compound (**D5**) as a yellow-orange oil (5.7 g; yield 81%).

MS; (ES) m/z: 176.1 $[MH^+]$. $C_{11}H_{13}NO$ requires 175.

1H-NMR (300 MHz, $CDCl_3$) δ: 8.32 (d,1H), 7.18 (1H, d), 3.31 (d, 2H), 2.85 (d, 2H), 2.67 (s, 3H), 2.43 (m, 1H), 1.22 (s, 3H).

Description 6

6-Bromo-2,7-dimethyl-5,6,7,8-tetrahydroquinoline-5-one (D6)

A solution of 2,7-dimethyl-5,6,7,8-tetrahydroquinoline-5-one (**D5**) (2 g; 11.4 mmol) in hydrobromic acid (12 mL of 48% in water) was treated dropwise with bromine (0.6 mL, 1 eq) at 60°C under vigorous stirring. The resulting mixture was stirred at 60°C for 1 h then evaporated *in vacuo* to give a waxy solid, which was triturated with a 1:1

solution of ether-isopropanol to afford the title product (**D6**) as a white powder (3 g; yield 100%).
MS; (ES) m/z: 254/256 [MH^+]. $C_{11}H_{12}NOBr$ requires 254.
1H-NMR (300 MHz, $CDCl_3$) δ: 8.79 (d,1H), 7.64 (d, 1H), 4.59 (d, 1H), 3.11 (s, 3H+2H), 2.37 (m, 1H), 1.31 (d, 3H).

Description 7
5-Hydroxy-2,7-dimethylquinoline (D7)
A mixture of 6-bromo-2,7-dimethyl-5,6,7,8-tetrahydroquinoline-5-one (**D6**) (3 g; 11.7 mmol), lithium carbonate (1.73 g, 2 eq.), lithium bromide (1.01 g, 1 eq.) and DMF (30 mL) was heated at 150°C under nitrogen for 2 h. The mixture was cooled and then evaporated *in vacuo*. The crude reaction mixture was twice purified through 50 g SCX columns to afford the title product (**D7**) as a yellow solid (1.3 g; 63%).
MS; (ES) m/z: 174.0 [MH^+].$C_{11}H_{11}NO$ requires 173.
1HNMR (600 MHz, DMSO) δ: 10.18 (s, 1H), 8.23 (d, 1H), 7.18 (d, 1H), 7.10 (s, 1H), 6.63 (s, 1H), 2.54 (s, 3H), 2.34 (s, 3H).

Description 8
(2,7-Dimethylquinolin-5-yl)piperazine (D8)
The title compound (**D8**) was prepared from 5-hydroxy-2,7-dimethylquinoline (**D7**) by the general methods described above for the preparation of **D3**.
1H-NMR (300 MHz, $CDCl_3$) δ: 8.35 (d, 1 H), 7.55 (s, 1 H), 7.20 (d, 1 H), 6.90 (s, 1 H), 3.15 (br m, 4 H), 3.05 (br m, 4 H), 2.75 (s, 3 H), 2.50 (s, 3 H), 2.30 (br s, 1 H).

Description 9
7-Chloro-2-methyl-5- piperazin-1-ylquinoline (D9)
The title compound (**D9**) was prepared from 7-chloro-5-hydroxy-2-methylquinoline (WO/0234754) according to the general method described for the preparation of **D3**.
MS; (ES) m/z: 262.1 [$MH]^+$. $C_{14}H_{16}ClN_3$ requires 261.
^{1}H-NMR (300 MHz, DMSO) δ: 8.36 (d, 1 H), 7.61 (d, 1 H), 7.40 (d, 1 H), 6.92 (d, 1H , 3.32 (m, 4 H), 2.93 (m, 4 H), 2.62 (s, 3 H).

Description 10
5-Fluoro-2-methyl-3,4-dihydroquinazoline (D10)
A stirred solution of 2-amino-6-fluorobenzylamine (1.1 g, 7.9 mmol) and triethyl orthoacetate (1.4 g, 8.6 mmol, 1.1 eq) in ethanol (30 mL) was heated at 80°C overnight. The reaction mixture was allowed to cool to r.t. and the solvent concentrated *in vacuo*. The crude reaction mixture was triturated with ether and filtered to afford the title compound (**D10**) as a white solid (0.74 g, yield 57%).
MS; (ES) m/z: 165.1 [MH^+]. $C_9H_9FN_2$ requires 164.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.1 (q, 1H), 6.7 (t, 2H), 4.7 (s, 2H), 2.0 (s, 3H).

Description 11

5-Fluoro-2-methylquinazoline (D11)

To a stirred solution of 5-fluoro-2-methyl-3,4-dihydroquinazoline (**D10**) (0.74 g, 4.5 mmol) in chloroform (100 mL) manganese dioxide (2.0 g, 23 mmol, 5 eq.) was added portionwise. The reaction mixture was stirred at r.t. overnight, then a further portion of manganese dioxide (2.0 g, 23 mmol, 5 eq.) was added and stirring continued for 6 h. The reaction mixture was then filtered through a celite pad, which was then washed with DCM (50 mL). The combined organics were concentrated *in vacuo* to afford the title compound (**D11**) as a yellow solid (0.72 g, yield 98%).

MS; (ES) m/z: 163.1 [MH^+]. $C_9H_7FN_2$ requires 162.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.6 (s, 1H), 7.8 (m, 2H), 7.2 (t, 1H), 2.9 (s, 3H).

Description 12

2-Methyl-5-piperazin-1-ylquinazoline (D12)

To a solution of 5-fluoro-2-methylquinazoline (**D11**) (2 g; 12.3 mmol) in dry DMF (10 mL) triethylamine (3.4 mL; 2 eq.) and piperazine (11 g; 10 eq.) were added. The reaction mixture was stirred under nitrogen at 120°C. for 4 h., then poured into water (10 mL) and extracted with ethyl acetate (5x15 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by SCX cartridge to afford the title compound (**D12**) as a yellow solid. (1.8 g; yield 64%).

MS; (ES) m/z: 229.2 [MH^+]. $C_{11}H_8F_3NO_3S$ requires 228.

1H-NMR (300 MHz, $CDCl_3$) δ: 9.58 (s, 1 H), 7.89 (t, 1 H), 7.62 (d, 1H), 7.27 (d, 1 H), 3.25 (m, 8H); 2.91 (s, 3H).

Description 13

2-Methyl-5-(3-methylpiperazin-1-yl)quinoline (D13)

2-Methylpiperazine (40.8 mg; 0.40 mmol; 1.2 eq.), cesium carbonate (164 mg; 0.5 mmol; 1.5 eq.), palladium acetate (6 mg; 0.028 mmol; 0.08 eq.) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (26 mg; 0.042 mmol; 0.12 eq.) were added to a solution of 2-methylquinolin-5-yltrifluoromethanesulfonate (**D1**) (100 mg, 0.34 mmol; 1 eq) in dry toluene (1.50 mL) under nitrogen. The reaction mixture was stirred at reflux under nitrogen for 8 h. A further addition of 2-methylpiperazine (40.8 mg; 0.40 mmol; 1.2 eq) and palladium acetate (6 mg; 0.028 mmol; 0.08 eq.) was then made to the reaction mixture followed by heating at reflux for a further 2h. The reaction was cooled to r.t. and quenched with a saturated aqueous solution of ammonium chloride (100 mL) and then extracted into ethyl acetate (3x50 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by SPE cartridge (Si, 2g), eluting with 5% methanol in dichloromethane to afford the title compound as a red oil (56 mg; yield 69%).

MS; (ES) m/z: 241.34 [$MH]^+$. $C_{15}H19N_3$ requires 242.4.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.36 (d, 1H), 7.77 (d, 1 H), 7.61 (t, 1 H), 7.29 (d, 1 H), 7.12 (d, 1 H), 3.45 (t, 1 H), 3.3- 2.8 (d/t, 1/1 H), 3.3- 3.1 (m/m, 1/1 H), 3.3- 2.75 (m/m, 1/1 H), 2.74 (s, 3 H), 1.36 (d, 3H).

Description 14

2-Methyl-5-(2-methylpiperazin-1-yl)quinoline (D14)

3-Methylpiperazine-1-carboxylic acid *tert*-butyl ester (160 mg; 0.80 mmol; 2 eq.) (prepared as reported in J. Med. Chem. 1993, 36, 690-698), cesium carbonate (195 mg; 0.6 mmol; 1.5 eq.), palladium acetate (9 mg; 0.04 mmol; 0.10 eq.) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (38 mg; 0.06 mmol; 0.15 eq.) were added to a solution of 2-methylquinolin-5-yl-trifluoromethanesulfonate (**D1**) (117 mg, 0.4mmol; 1 eq) in dry toluene (2.5 mL) under nitrogen. The reaction mixture was stirred at reflux under nitrogen for 10 h. The reaction was cooled and filtered through a pad ofcelite which was then washed with DCM (50 mL). The filtrates was concentrated *in vacuo* and the crude product was purified by SPE cartridge (Si, 2g), eluting with 5% ethylacetate in cyclohexane to afford 3-methyl-4-(2-methylquinolin-5-yl)piperazin-1-carboxylic acid *tert*-butyl ester as a yellow oil (84 mg; yield 62%). MS; (ES) m/z: 341.45 $[MH]^+$. $C_{20}H_{27}N_3O_2$ requires 342.4. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.5 (d, 1H), 7.77 (d, 1 H), 7.61 (t, 1 H), 7.29 (d, 1 H), 7.12 (d, 1 H), 3.8-3.6, m/m, 2H), 3.4- 3.3 (m, 1 H), 3.2- 3.1 (m, 1 H), 3.1-2.9 (m, 2H), 2.74 (s, 3 H), 1.45 (s, 9H), 1.36 (d, 3H). This compound (84 mg) was dissolved in a mixture 3:1 oftrifluoroacetic acid: DCM (4 mL) and stirred at r.t. for 6h. The solvent was evaporated *in vacuo* and the residue purified on SCX cartridge (1g) to afford the title compound (**D14**) (44 mg; yield 76%)
MS; (ES) m/z: 241.45 $[MH]^+$. $C_{15}H_{19}N_3$ requires 242.4.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.5 (d, 1H), 7.77 (d, 1 H), 7.61 (t, 1 H), 7.29 (d, 1 H), 7.12 (d, 1 H), 3.3 (m, 4H), 3.15 (m, 4 H), 2.74 (s, 3 H), 1.9 (m, 2H).

Description 15

2-Methyl-5-(3-methylpiperazin-1-yl)quinazoline (D15)

A solution of 2-methyl-5-fluoroquinazoline (100 mg; 0.616 mmol; 1eq), 2-methylpiperazine (310 mg; 3.083 mmol; 5eq) and triethylamine (0.17 mL; 1.23 mmol; 2 eq) in dry DMF (2.5 mL) was heated at 120°C for 5 h. The yellow solution was cooled and the solvent was evaporated *in vacuo.* The crude material was purified on SPE cartridge (Si; 2 g) eluting with a gradient from 100% dichloromethane to 85% dichloromethane :1% NH_4OH 2M sol in methanol to afford the title compound (**D15**) (85 mg; yield 57%).
MS; (ES) m/z: 243.3 $[MH^+]$. $C_{14}H_{18}N_4$ requires 242.32.
^{1}H NMR (300MHz, $CDCl_3$) δ: 9.48 (s, 1H), 7.81 (t, 1H), 7.48 (d, 1H), 7.10 (d, 1H), 3.03 (m, 1H), 3.23-2.98-2.76-2.41 (m, 6H), 2.72 (s, 3H) 1.01 (d, 3H).

Description 16

4-(2-Methylquinolin-5-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (D16)

A mixture of 1(2H)-pyridinecarboxylic acid, 3,6-dihydro-4-(4,4,5,5-tetramethyl-1,3,2 dioxaborolan-2-yl)-1,1-dimethylethyl ester (Tetrahedron Letters 2000, 41, 3705-3708) (0.56 g, 1.8 mmol), 2-methylquinolin-5-yl trifluoromethanesulfonate (D1) (0.5 g, 1.72 mmol), [1,1'-bis(diphenylphosphino)ferrocene]palladium(II)chloride (140 mg, 0,17 mmol) and potassium carbonate (0.713 g, 5.1 mmol) in dry DMF (20 mL) was heated at 80°C under nitrogen for 3h. The DMF was removed *in vacuo* and the residue partitioned between water (25 mL) and DCM (3x50 mL). The organic extracts were dried (Na_2SO_4) and chromatographed on silica (eluent 30% EtOAc/cyclohexane) to afford the title compound (**D16**) as a colourless oil (0.35 g, 63%).
MS; (ES) m/z: 325 [MH^+]. $C_{20}H_{24}N_2O_2$ requires 324.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.15 (d, 1 H), 7.90 (d, 1 H), 7.57 (t, 1 H), 7.22 (m, 2 H), 5.70 (br s, 1 H), 4.20 (br m, 2 H), 3.65 (m, 2 H), 2.70 (s, 3 H), 2.45 (br m, 2 H), 1.50 (s, 9 H).

Description 17

2-Methyl-5-(1,2,3,6-tetrahydropyridin-4-yl]quinoline (D17)

A solution of 4-(2-methylquinolin-5-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (**D16**) (150 mg, 0.46 mmol) in DCM (10 mL) was treated with trifluoroacetic acid (0.35 mL, 0.46 mmol), stirred for 30 minutes and then stirred atr.t. for 16h. The reaction mixture was made basic with saturated aqueous $NaHCO_3$ (10 mL), then the organics were separated, dried (Na_2SO_4) and evaporated to give the title compound (**D17**) as a white solid (85 mg, 83%).
MS; (ES) m/z: 225 [MH^+]. $C_{15}H_{16}N_2$ requires 224.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.25 (d, 1 H), 7.87 (d, 1 H), 7.58 (t, 1 H), 7.23 (m, 2 H), 5.75 (br m, 1 H), 3.57 (m, 2 H), 3.25 (m, 2 H), 2.70 (s, 3 H), 2.40 (m, 2 H). NH not observed.

Description 18

4-(2-Methylquinolin-5-yl)piperidine-1-carboxylic acid *tert*-butyl ester (D18)

A solution of 4-(2-methylquinolin-5-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid *tert*-butyl ester (**D16**) (200 mg, 0.62 mmol) in ethanol (10 mL) was hydrogenated over 10% Pd-C (20 mg) at atmospheric pressure for 20 h atr.t. The reaction mixture was filtered through a celite pad which was then washed with ethanol (2x50 mL). The combined filtrates were then evaporated to give the title compound (**D18**) asa clear colourless oil (150 mg, 74%).
MS; (ES) m/z: 327 [MH^+]. $C_{20}H_{26}N_2O_2$ requires 326.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.20 (d, 1 H), 7.80 (d, 1 H), 7.55 (t, 1 H), 7.20 (m, 2 H), 4.20 (br m, 2 H), 3.25 (br m, 1 H), 2.85 (br m, 1 H), 2.65 (s, 3 H), 1.85 (br m, 2 H), 1.65 (br m, 2 H), 1.40 (s, 9 H), 1.38 (m, 1 H).

Description 19

2-Methyl-5-piperidin-4-ylquinoline (D19)

The title compound (**D19**) was prepared in a similar fashion to Description 17 starting from 4-(2-methylquinolin-5-yl)piperidine-1-carboxylic acid *tert*-butyl ester (**D18**) (138 mg, 0.42 mmol) as a pale yellow oil (69 mg, 72%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.25 (d, 1 H), 7.85 (d, 1 H), 7.60 (t, 1 H), 7.35 (d, 1 H), 7.25 (d, 1 H), 3.10-3.40 (m, 3 H), 2.85 (t, 2 H), 2.70 (s, 3 H), 1.85 (br d, 2 H), 1.60-1.80 (m, 2 H). MH not observed.

Description 20

4-(2-Methylquinolin-5-yl)-[1,4]diazepane-1-carboxylic acid *tert*-butyl ester (D20)

Homopiperazine (160 mg; 0.80 mmol; 2 eq.) (prepared as reported in J. Med. Chem. 1993, 36, 690-698), cesium carbonate (195 mg; 0.6 mmol; 1.5 eq.), palladium acetate (9 mg; 0.04 mmol; 0.10 eq.) and 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (38 mg; 0.06 mmol; 0.15 eq.) were added to a solution of 2-methylquinolin-5-yl-trifluoromethanesulfonate (**D1**) (117 mg, 0.4 mmol; 1 eq) in dry toluene (2.5 mL) under nitrogen. The reaction mixture was stirred at reflux under nitrogen for 10 h then cooled and filtered through a celite pad which was then washed with DCM (2x50 mL). The combined filtrates were concentrated *in vacuo* and the crude product was purified by SPE cartridge (Si, 2g), eluting with 5% ethylacetate in cyclohexane affording the title compound (**D20**) as a yellow oil (84 mg; yield 62%).

MS; (ES) m/z: 341.45 $[MH]^+$. $C_{20}H_{27}N_3O_2$ requires 342.4.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.5 (d, 1H), 7.77 (d, 1 H), 7.61 (t, 1 H), 7.29 (d, 1 H), 7.12 (d, 1 H), 3.8-3.6, m/m, 2H), 3.4- 3.3 (m, 1 H), 3.2- 3.1 (m, 1 H), 3.1-2.9 (m, 2H), 2.74 (s, 3 H), 1.45 (s, 9H), 1.36 (d, 3H).

Description 21 (D21)

5-[1,4]Diazepan-1-yl-2-methylquinoline (D21)

4-(2-Methylquinolin-5-yl)-[1,4]diazepane-1-carboxylic acid *tert*-butyl ester (**D20**) (51 mg) was dissolved in a mixture 3:1 of trifluoroacetic acid/DCM (4 mL) and stirred at r.t. for 6h. The solvent was evaporated *in vacuo* and the residue purified on SCX cartridge (1g) to afford the title compound (**D21**) (35 mg; yield 85%).

MS; (ES) m/z: 241.45 $[MH]^+$. $C_{15}H_{19}N_3$ requires 242.4.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.5 (d, 1H), 7.77 (d, 1 H), 7.61 (t, 1 H), 7.29 (d, 1 H), 7.12 (d, 1 H), 3.3 (m, 4H), 3.15 (m, 4 H), 2.74 (s, 3 H), 1.9 (m, 2H).

Description 22

5-[1,4]Diazepan-1-yl-2-methylquinazoline (D22)

A solution of 5-fluoro-2-methylquinazoline (**D11**) (100 mg; 0.616 mmol; 1eq), homopiperazine (309 mg; 3.083 mmol; 5eq) and triethylamine (0.17 mL; 1.23 mmol; 2 eq.) in dry DMF (2.5 mL) was heated at 120°C for 5 h. The yellow solution was cooled and the solvent evaporated *in vacuo.* The residue was dissolved in ethylacetate (20 mL) and washed with brine (3x 15 mL). The organic layers were

combined, dried (Na_2SO_4) and concentrated *in vacuo.* The crude material was purified on SPE cartridge (Si; 2g) eluting with a gradient from 100% DCM to 85% DCM 1% NH_4OH 2M sol in methanol to afford the title compound (**D22**) (50 mg; yield 35%).

MS; (ES) m/z: 243.3 [MH^+]. $C_{14}H_{18}N_4$ requires 242.32.

^1H NMR (300MHz, $CDCl_3$) δ: 9.5 (s, 1H), 7.7 (t, 1H), 7.45 (d, 1H), 7.05 (d, 1H), 3.45 (t, 4H), 3.1 (t, 4H), 2.85 (s, 3H) 2.05 (5, 2H).

Description 23

6-(2-Chloroethanoyl)-7-fluoro-4*H*-benzo[1,4]oxazin-3-one (D23)

Aluminum chloride (1.9 g; 2.2 eq) and chloroacetyl chloride (0.6 mL; 1.2 eq) were added at r.t. to a suspension of 7-fluoro-4H-benzo[1,4]oxazin-3-one (1.1 g; 6.58 mmol) in dry 1,2-dichloroethane (10 mL). The reaction mixture was stirred at 80°C under nitrogen for 3 h, then poured into a saturated aq. solution of ammonium chloride (10 mL) and extracted into ethyl acetate (3x10 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo.* The crude product was purified by flash chromatography on silica gel, eluting with 60% ethyl acetate in cyclohexane to afford the title compound (**D23**) as a white solid (0.8 g; yield 50%).

MS; (ES) m/z: 244.1 [MH^+]. $C_{10}H_7ClFNO_3$ requires 243.

^1H-NMR (300 MHz, DMSO) δ: 10.58 (s, 1 H), 7.41 (d, 1H), 7.05 (d, 1 H), 7.48 (d, 1 H), 4.95 (d, 2 H), 4.74 (s, 2 H).

Description 24

6-(2-Chloroethyl)-7-fluoro-4*H*-benzo[1,4]oxazin-3-one (D24)

The title compound (**D24**) was prepared in 72% yield according to the experimental procedure described for **D4** starting from 6-(2-chloroethanoyl)-7-fluoro-4*H*-benzo[1,4]oxazin-3-one (**D23**).

MS; (ES) m/z: 230.2 [$MH]^+$. $C_{10}H_9ClFNO_2$ requires 229.

^1H-NMR (300 MHz, DMSO) δ: 10.72 (s, 1 H), 6.87 (d, 1H), 6.81 (d, 1H), 4.56 (s, 2 H), 3.77 (t, 2 H), 2.96 (t, 2 H).

Description 25

(4-Bromo-2-nitro-phenoxy)acetic acid methyl ester (D25)

A mixture of 4-bromo-2-nitro-phenol (6.0 g, 27.5 mmol), methyl bromoacetate (5.0 g, 33 mmol), anhydrous potassium carbonate (4.6 g, 33.3 mmol) in DMF (70 mL) was stirred at 50°C for 4h. The solvent was removed under vacuum and then the residue was co-evaporated with toluene (3 x 20 mL), dissolved in DCM (150 mL), washed with water (2 x 50 mL), 1N sodium hydroxide (1 x 50 mL), water (2 x 50 mL) and dried ($MgSO_4$). The solvent was evaporated to give the title compound (**D25**) as a yellow solid (7.9 g, 99% yield); δ_H (400 MHz, $CDCl_3$), 3.81(3H, s) 4.78(2H, s), 6.89(1H, d, *J* 8.8 Hz), 7.63(1H, dd, *J* 8.8Hz, 2.5 Hz), 8.00(1H, *J* 2.5 Hz).

Description 26

(4-Allyl-2-nitrophenoxy)acetic acid methyl ester (D26)

(4-Bromo-2-nitro-phenoxy)acetic acid methyl ester (**D25**) (6.8 g, 23.5 mmol), allyl tributyl tin (12 g, 36.2 mmol), tetrakis(triphenylphosphine)palladium(0) (1.39 g, 1.2 mmol) in toluene (100 mL), was stirred at 110°C for 8h under argon. The solvent was removed and the residue was dissolved in acetonitrile (300 mL) and washed with petroleum ether (40-60°C) (4 x 100 mL). The acetonitrile was evaporated and the crude product was purified by column chromatography on silica gel (eluting with ethyl acetate–hexane gradient) to give the title compound (**D26**) as a tan oil (4.0 g, 68% yield); MS: m/z (MH^+) = 252/253.

Description 27

[4-(3-Hydroxypropyl)-2-nitrophenoxy]acetic acid methyl ester (D27)

To a solution of (4-allyl-2-nitrophenoxy)acetic acid methyl ester (**D26**) (2.0 g, 8.0 mmol), in THF (30 mL) at 0°C, was added borane-tetrahydrofurane complex (10 mL, 1M solution in THF) dropwise over a period of 2h. The mixture was stirred at 5-8°C for 1.5 h, treated with water (15 mL, added slowly), then with sodium perborate tetrahydrate (2.0 g, 13 mmol). The resulting mixture was stirred vigorously at r.t. for 2.5h, concentrated to a small volume and the residual water solution was extracted with ethyl acetate (4 x 20 mL). The combined extracts were dried ($MgSO_4$), the solvent was evaporated and the product was purified by column chromatography on silica gel (eluting with ethyl acetate-dichloromethane gradient) to give the title compound (**D27**) as a slightly tan oil (0.5g, 100% pure and 0.166 g mixture of the title compound and the corresponding secondary alcohol, ratio 8:2; 30% yield); MS: m/z (MH^+) = 270/271.

Description 28

[4-(3-Methanesulfonyloxypropyl)-2-nitrophenoxy]acetic acid methyl ester (D28)

To a stirred solution of 4-(3-hydroxypropyl)-2-nitrophenoxy]acetic acid methyl ester (**D27**) (0.5 g, 1.9 mmol) and triethylamine (0.46 g, 4.5 mmol) in DCM (20 mL) at 0°C was added a solution of methanesulfonyl chloride (0.33 g, 2.9 mmol) in dichloromethane (5 mL), this was then stirred at 5°C for 3h. The mixture was diluted with DCM (80 mL), washed with saturated aqueous sodium hydrogen carbonate (2 x 30 mL), water (1 x 30 mL) and dried ($MgSO_4$). The solvent was evaporated to give the title compound (**D28**) as a cream solid (0.56 g, 87% yield); MS: m/z (MH^+) = 348.

Description 29

(4-{3-[4-(2-Methylquinolin-5-yl)piperazin-1-yl]propyl}-2-nitrophenoxy)-acetic acid methyl ester (D29)

A mixture of [4-(3-methanesulfonyloxypropyl)-2-nitrophenoxy]acetic acid methyl ester (**D28**) (0.21 g, 0.6 mmol), 2-methyl-5-piperazin-1-ylquinoline (**D3**) (0.23 g, 1 mmol), anhydrous potassium carbonate (0.21 g, 1.5 mmol), sodium iodide (0.09 g, 0.6 mmol), and molecular sieves (0.4 g, 4A) in DMF (10 mL) was stirred at 80°C for 1.5h.

The solvent was evaporated, the residue was dissolved in DCM (100 mL) and washed with water (2 x 20 mL). The solvent was evaporated and the product was purified by column chromatography on silica gel (eluting with methanol-dichloromethane gradient) to give the title compound (**D29**)as a tan oil, (0.2 g, 69% yield); MS: m/z (MH^+) = 479/481.

Description 30

7-Fluoro-2-methyl-5-piperazin-1-ylquinoline (D30)

A solution of 5,7-difluoro-2-methylquinoline (WO/0234754) (1.2 g, 6.70 mmol) and piperazine (2.5 eq) in dry DMSO (10 mL) was stirred at 95°C under nitrogen for 24 h. The reaction mixture was worked-up using an SCX cartridge and the residue then purified by flash chromatography on silica gel, eluting with 3% methanol in DCM to afford the title compound (**D30**) as a yellow solid (0.8 g; yield 30%).

MS; (ES) m/z: 246.3 [MH^+]. $C_{14}H_1IFN_3$ requires 245.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.30 (d, 1 H), 7.32 (dd, 1 H), 7.19 (d, 1H), 6.82 (dd, 1 H), 3.14 (m, 4 H), 3.05 (m, 4 H), 2.70 (s, 3H).

Description 31

6-(8-Hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)-4*H*-benzo[1.4]oxazin-3-one (D31)

A stirred solution of 6-bromo-4*H*-benzo[1,4]oxazin-3-one (0.5 g, 2.2 mmol, 1.0 eq.) in dry THF (4 mL) was cooled to –30°C and a 1.6 M solution of n-butyllithium in hexanes (3 mL, 4.8 mmol, 2.2 eq) was added dropwise. The reaction mixture was stirred for 0.5 h then a solution of 1,4-dioxaspiro[4.5]decan-8-one (0.75 g, 4.8mmol, 2.2 eq) in dry THF (4 mL) was added dropwise. The reaction mixture was stirred at –30°C for 1 h, then a saturated aq. solution of ammonium chloride (20 mL) was added and the mixture was extracted with ethyl acetate (3x20 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with 50% ethyl acetate in cyclohexane, to give the title compound (**D31**) as a yellowish solid (0.101 g, yield 15%).

MS; (ES) m/z: 306 [MH^+]. $C_{16}H_{19}NO_5$ requires 305.

^{1}H-NMR (500 MHz, DMSO) δ: 10.59 (s, 1H), 7.04 (d, 1H), 6.96 (dd, 1H), 6.84 (d, 1H), 4.85 (s, 1H), 4.51 (s, 2H), 3.87 (s, 4H), 1.88 (m, 4H), 1.6 (m, 2H), 1.5 (m, 2H).

Description 32

6-(4-Oxocyclohex-1-enyl)-4H-benzo[1,4]oxazin-3-one (D32)

A solution of 6-(8-hydroxy-1,4-dioxaspiro[4.5]dec-8-yl)-4*H*-benzo[1.4]oxazin-3-one (**D31**) (84 mg, 0.28 mmol) in trifluoroacetic acid (4 mL) was stirred at r.t. for 1h. The reaction mixture was concentrated *in vacuo*, then the residue was disolved in ethyl acetate (20 mL) and treated with a saturated aq. solution of sodium hydrogencarbonate (20 ml). The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound (**D32**) as a white solid (58 mg, yield 87%).

MS; (ES) m/z: 244 [MH^+]. $C_{14}H_{13}NO_3$ requires 243.
^{1}H-NMR (300 MHz, DMSO) δ: 10.70 (s, 1H), 7.05 (d, 1H), 6.95 (m, 2H), 6.0 (m, 1H), 4.55 (s, 2H), 3.02 (m, 2H), 2.75 (m, 2H), 2.5 (m, 2H).

Description 33
Benzoic acid 4-methoxycarbonylmethoxy-3-nitrophenyl ester (D33)
A suspension of 4-hydroxyphenyl benzoate (24.7 g, 0.115 mol) in acetic acid (500 mL) was cooled (ice/water bath) and treated dropwise with nitric acid (90%, 7.3 mL, 0.173 mol) over 10 minutes whilst maintaining the temp below 20°C. The mixture was then stirred at r.t. for 16h. The mixture was reduced *in vacuo* and the residue triturated with water for 3h. The resultant yellow solid was filtered off and dried (29.3 g, 98%). A solution of this solid (20.0 g, 0.077 mol) in acetone (400 mL) was treated with potassium carbonate (16.0 g, 0.116 mol) and methyl bromoacetate (11.0 mL, 0.116 mol) and heated at reflux for 16h. The solvent was removed *in vacuo* and the residue partitioned between aq. $NaHCO_3$ (250 mL) and DCM (4 x 200 mL). The combined organics were dried (Na_2SO_4) and evaporated to a buff solid which was triturated with 40-60° petrol to afford the title compound (D33) as a buff powder (12.7 g, 50%).
MS; (ES) m/z: 332 [MH^+]. $C_{16}H_{13}NO_7$ requires 331.
1H-NMR (300 MHz, $CDCl_3$) δ: 8.15 (m, 2 H), 7.80 (m, 1 H), 7.60 (t, 1 H), 7.50 (t, 2 H), 7.40 (dd, 1 H), 7.05 (d, 1 H), 4.77 (s, 2H), 3.80 (s, 3H).

Description 34
(4-Hydroxy-2-nitrophenoxy)acetic acid methyl ester (D34)
A suspension of benzoic acid 4-methoxycarbonylmethoxy-3-nitrophenyl ester (**D33**) (10.5 g, 0.03 mol) in methanol (200 mL) was treated dropwise with a solution of sodium methoxide (1.8 g, 0.033 mol) in methanol (100 mL) over 20 minutes. The resulting solution was stirred at r.t. for 3h, reduced *in vacuo* to *ca.*100 mL and partitioned between water (300 mL) and Et_2O:cyclohexane (1:5, 200 mL). The aqueous phase was separated, acidified (1N HCl to pH 5-6) and extracted with DCM (3 x 250 mL). The combined organics were dried (Na_2SO_4), evaporated *in vacuo* and triturated with Et_2O:cyclohexane (1:3, 100 mL) to afford the title compound (**D34**) as an orange solid 4.35 g, 64%.
1H-NMR (300 MHz, $CDCl_3$) δ: 7.33 (d, 1 H), 6.97 (m, 2 H), 5.35 (br s, 1 H), 4.67 (s, 2 H), 3.80 (s, 3 H).

Description 35
[4-(2-Bromoethoxy)-2-nitrophenoxy]acetic acid methyl ester (D35)
A solution of (4-hydroxy-2-nitrophenoxy)acetic acid methyl ester (**D34**) (0.50 g, 2.20 mmol) in DMF (10 mL) was treated with potassium carbonate (1.5 g, 11.0 mmol) and 1,2-dibromoethane (1.9 mL, 22.0 mmol). The mixture was heated at 85°C for 6 h, evaporated *in vacuo* and the residue partitioned between water (50 mL) and DCM (3 x 50 mL). The combined organics were dried (Na_2SO_4), evaporated *in vacuo* and the

residue chromatographed on silica gel (eluent 10% EtOAc/cyclohexane to 20% EtOAc/cyclohexane) to afford a yellow oil (0.51 g, 69%).
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 7.33 (d, 1 H), 7.07 (m, 1 H), 6.97 (d, 1 H), 4.70 (s, 2 H), 4.25 (t, 2 H), 3.75 (s, 3 H), 3.60 (t, 2 H).

Description 36

6-(2-Bromoethoxy)-4*H*-benzo[1,4]oxazin-3-one (D36)

A mixture of [4-(2-bromoethoxy)-2-nitrophenoxy]acetic acid methyl ester (**D35**) (200 mg, 0.60 mmol) and iron powder (230 mg, 4.20 mmol) in acetic acid (5 mL) was stirred at room temp under nitrogen for 3 h. Water (10 mL) was added, the mixture basified (K_2CO_3) and the resultant dark green solution extracted with DCM (3 x 30 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to afford the title compound (**D36**) a white solid (128 mg, 79%).
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.35 (br s, 1 H), 6.88 (d, 1 H), 6.50 (d, 1 H), 6.40 (s, 1 H), 4.55 (s, 2 H), 4.20 (t, 2 H), 3.55 (t, 2 H).
MS; (ES) m/z: 272/274 [MH^+]. $C_{10}H_{10}NO_3$ requires 272.

Description 37

2-Chloro-1-(5-chloro-2-fluoro-4-hydroxyphenyl)ethanone (D37)

To a solution of 1-chloro-4-fluoro-2-methoxy-benzene (12.9 g, 80 mmol) in 1,2-dichloroethane (80 mL) at room temperature, chloroacetyl chloride (7.7 mL, 96mmol) and aluminium trichloride (21.4 g, 0.16 mmol) were added. The solution was heated to 70°C and stirred at this temperature for 3h under nitrogen. After cooling to room temperature, the reaction mixture was carefully poured onto crushed ice and extracted with DCM (2 x 150 mL). Washing of the organic layers with brine (200 mL) followed by drying (Na_2SO_4) and removal of the solvent *in vacuo* afforded a crude which was purified by flash chromatography eluting with 20% cyclohexane in ethyl acetate. The oil collected (8 g) was a mixture containing the title compound together with 2-chloro-4-(2-chloro-acetyl)-5-fluoro-phenyl chloroacetate. The mixture (7.8 g) was dissolved in methanol (100 mL) and a 2M aqueous solution of sodium carbonate (45 mL) was added. The solution was stirred at room temperature for 1h then the organic solvent was removed under vacuum and the remaining solution was acidified with a 5% aqueous solution of HCl, extracted with DCM (120 mL), washed with brine (80 mL) and dried (Na_2SO_4). Removal of the solvent *in vacuo* afforded the title compound (**D37**) as a brown solid (6.8 g, 38%).
MS; (EI) m/z: 222 [$M]^+$. $C_8H_5Cl_2FO_2$ requires 222.
^{1}H-NMR (500 MHz, DMSO-d^6) δ: 11.8 (bs, 1H), 7.87 (d, 1H), 6.83 (d, 1H), 4.94 (d, 2H)

Description 38

2-Chloro-4-(2-chloroethyl)-5-fluorophenol (D38)

A solution of 2-chloro-1-(5-chloro-2-fluoro-4-hydroxyphenyl)ethanone (**D37**) (5.73 g, 25.7 mmol) in trifluoroacetic acid (25 mL) was cooled to 0°C and triethylsilane (9.03

mL, 56.5 mmol) was added dropwise. The mixture was allowed to warm to room temperature and then stirred under nitrogen for 2h. The reaction mixture was concentrated *in vacuo* diluting repeatedly with ethyl acetate. The crude mixture was slowly poured onto crushed ice and solid sodium carbonate and basified further with a 5% aqueous solution of NaOH. The aqueous layer was separated from the organic layer, cooled at 0°C, acidified with a 10% aqueous solution of HCl and extracted with dichloromethane (150 mL). Drying (Na_2SO_4) and evaporation of the solvent under vacuum afforded the title compound (**D38**) as a dark brown oil (2.38 g, 42%).
MS; (EI) m/z: 208 $[M]^+$. $C_8H_5Cl_2FO_2$ requires 208.
^{1}H-NMR (500 MHz, DMSO-d^6) δ: 10.51 (bs, 1H), 7.33 (d, 1H), 6.70 (d, 1H), 3.73 (t, 2H), 2.90 (t, 2H).

Description 39
6-Chloro-4-(2-chloroethyl)-3-fluoro-2-nitrophenol (D39)
A solution of 2-chloro-4-(2-chloroethyl)-5-fluorophenol (**D38**) (1.95g, 9.3mmol) in glacial acetic acid (10 mL) was cooled to 0°C and 90% nitric acid (0.48 mmol, 1.03 mmol) was added dropwise. After 45 min of stirring at 0°C the reaction mixture was poured onto crushed ice, extracted with ethyl acetate (2 x 100 mL) and the organic layers washed with water (100 mL) and brine (100 mL) and dried (Na_2SO_4). The solvent was removed *in vacuo* giving a crude brown oil, which was purified by flash chromatography eluting with 33% ethyl acetate in cyclohexane. The title compound (**D39**) was obtained as an orange solid (1.66g, 70%).
MS; (EI) m/z: 253 $[M]^+$. $C_8H_5Cl_2FO_2$ requires 253.
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.6 (d, 1H), 3.7 (t, 2H), 3.10 (td, 2H).

Description 40
2-Amino-4-(2-chloroethyl)-3-fluorophenol (D40)
A mixture of 10% w/w palladium on carbon (0.200g, 20% w/w) and 6-chloro-4-(2-chloroethyl)-3-fluoro-2-nitrophenol (**D39**) (1g, 3.9 mmol) in absolute ethanol (12 mL) was hydrogenated at atomospheric pressure with vigorous stirring for 8h. A further addition of 10% w/w palladium on carbon (0.1g, 10% w/w) was made and the stirred suspension was left under a hydrogen atmosphere for another 16h. The catalyst was filtered off washing the filter with ethanol and the solvent was removed *in vacuo* affording the title compound (**D40**) as a white solid (0.75 g, quantitative yield).
MS; (ES) m/z: 190.6 $[MH]^+$. C_8H_9ClFO requires 189.
^{1}H-NMR (500 MHz, DMSO-d^6) δ: 10.80 (bs, 1H), 6.95 (t, 1H), 6.75 (dd, 1H), 8.0÷6.0 (broad, 2H), 3.75 (t, 2H), 2.95 (t, 2H)

Description 41
6-(2-Chloroethyl)-5-fluoro-4*H*-benzo[1,4]oxazin-3-one (D41)
A solution of chloroacetyl chloride (0.23 mL, 2.9 mmol) in dry THF (1.5 mL) was added dropwise to a stirred mixture of 2-amino-4-(2-chloroethyl)-3-fluorophenol (**D40**) (0.500 g, 2.6 mmol) and solid sodium hydrogen carbonate (0.49 g, 5.9 mmol)

in dry THF (6 mL) under nitrogen at 0°C. After 30 min. of stirring at 0°C, the solvent was removed under vacuum and the residue was dissolved in butan-2-one (2.5 mL) and water (2.5 mL). Solid potassium carbonate (0.800g, 5.9 mmol) was added and the reaction mixture was heated at reflux for 1h. The mixture was then diluted with ethyl acetate (15 mL) and washed with water (15 mL) and brine (15 mL) and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* gave a crude yellow solid which was purified by flash chromatography eluting with 33% ethyl acetate in cyclohexane affording the title compound (**D41**) as a white solid (0.320 g, 71%).
MS; (ES) m/z 230.6 $[MH]^+$. $C_{10}H_9ClFNO_2$ requires 229.
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.00 (bs, 1H), 6.80 (t, 1H), 6.72 (d, 1H), 4.55 (s, 2H), 3.67 (t, 2H), 3.03 (t, 2H).

Description 42

6-(2-Chloroethyl)-5-fluoro-4-methyl-4*H*-benzo[1,4]oxazin-3-one (D42)

6-(2-Chloroethyl)-5-fluoro-4*H*-benzo[1,4]oxazin-3-one (**D41**) (0.1 g, 0.43 mmol) was dissolved in dry DMF (1 mL). The solution was cooled to 0°C and 60% w/w sodium hydride dispersion in mineral oil (0.019 g, 0.48 mmol) was added under nitrogen. The solution was stirred at that temperature for 10 minutes then methyl iodide (0.041 mL, 0.65 mmol) was added. The reaction was allowed to warm to room temperature and stirred for 30 min. The reaction mixture was diluted with DCM (15 mL), washed with water (2x10 mL) and brine (10 mL) and dried (Na_2SO_4). Removal of the solvent *in vacuo* afforded a crude which was purified by flash chromatography eluting with 33% ethyl acetate in cyclohexane affording the title compound (**D42**) as a white solid (0.080 g, 75%).
MS; (ES) m/z 244.6 $[MH]^+$. $C_{24}H_{25}FN_4O_2$requires 243.
^{1}H-NMR (500 MHz, $CDCl_3$) δ: 6.80 (t, 1H), 6,70 (d, 1H) 4.50 (s, 2H), 3.70 (t, 2H), 3,50 (d, 3H), 3.10 (td, 2H).

Description 43

6-(2-Chloroethyl)-4-methyl-4*H*-benzo[1,4]oxazin-3-one (D43)

To a solution of 6-(2-chloroethyl)-4*H*-benzo[1,4]oxazin-3-one (**D4**) (1.0 g, 4.74 mmol) in THF, at 0°C, a 60%w/w suspension of NaH in mineral oil (240mg, 1.5eq.) was added in portions. After 40 minutes iodomethane (0.31 mL) was added and the reaction was allowed to reach room temperature and left overnight. The reaction was quenched with a saturated aqueous solution of NH_4Cl, diluted with ethyl acetate, washed with brine, dried (Na_2SO_4) and concentrated under vacuum. The crude was purified by chromatography eluting with 20% ethyl acetate in cyclohexane affording the title compound **(D43)** as a white solid (840mg, 79%).
MS; (ES) m/z: 226.6 $[MH]^+$. $C_{11}H_{12}ClNO_2$ requires 225.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.85 (d, 1 H), 6.78 (dd, 1 H), 6.73 (d, 1 H), 4.55 (s, 2 H), 3.60 (t, 2 H), 3.30 (s, 3 H), 2.98 (t, 2 H).

Description 44

6-(2-Chloroethyl)-4-ethyl-4*H*-benzo[1,4]oxazin-3-one (D44)

To a solution of 0.5g of 6-(2-chloroethyl)-4*H*-benzo[1,4]oxazin-3-one (**D4**) (2.37 mmol) in THF (15ml), at 0°C a 60% w/w suspension of NaH in mineral oil (1190 mg, 1.5eq.) was added in portions. After 40 minutes of iodomethane (199□L, 1.05eq.) was added and the reaction was allowed to reach room temperature and then brought to reflux. The reaction was quenched with a saturated aqueous solution of NH_4Cl, diluted with ethyl acetate, washed with brine, dried (Na_2SO_4) and concentrated under vacuum. The crude was purified by chromatography eluting with 20% ethyl acetate in cyclohexane affording the title compound (**D44**) as a pale yellow solid (400 mg, 71%).

MS; (ES) m/z: 240 $[MH]^+$. $C_{12}H_{14}ClNO_2$ requires 239.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 6.90 (d, 1 H), 6.75 (d+s, 2 H), 4.55 (s, 2 H), 3.95 (q, 2 H), 3.50 (t, 2 H), 2.90 (t, 2 H), 1.05 (t, 3H).

EXAMPLES

General procedure for the alkylation of arylpiperazines with 6-(2-chloroethyl)-4*H*-benzo[1,4]oxazin-3-one (D4)

To a suspension of the appropriate arylpiperazine in MIBK or NMP as solvent, 6-(2-chloroethyl)-4*H*-benzo[1,4]oxazin-3-one (**D4**) (1.3 eq), NaI (1.3 eq), Na_2CO_3 (1.3 eq) were added. The reaction mixture was heated at 120°C for 12 h. and the solvent removed by SCX cartridge. The crude material was purified on SPE cartridge (Si) eluting with a gradient from 100% DCM to 80% DCM 20% MeOH to afford the final compounds (yields ranged from 16 to 85%). The free bases were generally converted into the hydrocloride salt by dissolving in MeOH or diethylether and adding 1M solution of hydrochloric acid (3 eq.).in dry MeOH. The final salts were then recovered by filtration.

Example 1

6-{2-[4-(2-Methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt (E1)

The title compound (**E1**) was prepared in 65% yield according to the general alkylation procedure starting from 2-methyl-5-piperazin-1-ylquinoline (**D3**).

MS; (ES) m/z: 403.2 $[MH]^+$. $C_{24}H_{26}N_4O_2HCl$ requires 402.

^{1}H-NMR (500 MHz, DMSO) δ: 11.05 (bs, 1 H), 10.81 (s, 1 H), 8.88 (bs, 1 H), 7.92 (bs, 2 H), 7.79 (bs, 1 H), 7.42 (s, 1 H), 6.95 (d, 1 H), 6.86 (dd, 1 H), 6.80 (d, 1 H), 4.55 (s, 2 H), 3.70 (d, 2 H), 3.6-3.5 (m, 4 H), 3.35 (m, 2 H), 3.35 (m, 2 H), 3.05 (m, 2 H), 2.88 (bs, 3 H).

Example 2

6-{2-[4-(2,7-Dimethylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloride salt (E2)

The title compound (**E2**) was prepared from (2,7-dimethylquinolin-5-yl)piperazine (**D8**) according to the general procedure described above in 30% yield.

1H-NMR (300 MHz, $CDCl_3$) δ: 8.50 (br s, 1 H), 8.25 (d, 1 H), 7.50 (s, 1 H), 7.15 (d, 1 H), 6.80-6.90 (m, 3 H), 6.65 (s, 1 H), 4.55 (s, 2 H), 3.10 (br s, 4 H), 2.75 (br s, 4 H), 2.68 (m, 2 H), 2.65 (s, 3 H), 2.47 (s, 3 H), 1.80 (br m, 2 H).

Example 3

6-{2-[4-(7-Chloro-2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloride salt (E3)

The title compound (**E3**) was prepared in 40% yield according to the general procedure from 7-chloro-2-methyl-5-piperazin-1-ylquinoline (**D9**).

MS; (ES) m/z: 437.1 $[MH]^+$. $C_{24}H_{25}ClN_4O_2HCl$ requires 436.

^{1}H-NMR (500 MHz, DMSO) δ: 10.90 (s, 1 H), 11.10 (s, 1 H), 8.50 (d, 1 H), 7.80 (s, 1H), 7.60 (d, 1 H), 7.40 (s, 1 H), 7.00 (d, 1 H), 6.80 (d, 1 H), 4.50 (s, 2 H), 3.80-3.00 (m, 4 H), 3.10-2.80 (m, 8 H), 2.70 (s, 3 H).

Example 4
6-[2-(4-Quinolin-4-ylpiperazin-1-yl)ethyl]-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt (E4)

The title compound (**E4**) was prepared from 4-piperazin-1-ylquinoline as above in 16% yield.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.02 (brs, 1 H), 8.70 (d, 1 H), 8.00 (m, 2 H), 7.60 (t, 1 H), 7.45 (t, 1 H), 6.80-6.90 (m, 3 H), 6.67 (s, 1 H), 4.55 (s, 2 H), 3.25 (br s, 4 H), 2.75 (br s, 4 H), 2.65 (m, 2 H), 1.85 (br m, 2 H).

Example 5
6-{2-[4-(2-Methylquinazolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt (E5)

The title compound (**E5**) was prepared in 85% yield according to the general procedure starting from 2-methyl-5-piperazin-1-ylquinazoline (**D12**).
MS; (ES) m/z: 403 [MH^+].
^{1}H-NMR (500 MHz, DMSO) δ: 11.4 (s, 1 H), 10.81 (s, 1 H), 9.58 (s, 1H), 7.89 (t, 1 H), 7.61 (d, 1H); 7.27 (d, 1H); 6.94 (d, 1H); 6.85 (dd, 1H); 6.81 (d, 1H); 4.54 (s, 2H); 3.68 (d, 2H); 3.56 (d, 2H); 3.47 (m, 2H); 3.36 (m, 2H); 3.33 (m, 2H); 3.07 (m, 2H); 2.77 (s, 3H).

Example 6
6-{2-[4-(2,3-Dihydrobenzo[1,4]dioxin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt (E6)

The title compound was prepared in 30% yield according to the general procedure starting from 1-(2,3-dihydrobenzo[1,4]dioxin-5-yl)piperazine.
MS; (ES) m/z: 396 [MH^+].
^{1}H-NMR (500 MHz, DMSO) δ: 10.63 (s, 1 H), 6.84 (m, 2H); 6.7 (m, 2H); 6.58 (m, 2H); 6.46 (m 2H); 4.51 (s, 2H); 4.20 (m, 4H); 2.95 (m, 4H); 2.54 (m, 4H); 2.63-2.54 (m, 4H).

Example 7
6-{2-[4-(6-Methoxyquinolin-8-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt (E7)

The title compound (**E7**) was prepared in 19% yield according to the general procedure starting from 6-methoxy-8-piperazin-1-ylquinoline.
MS; (ES) m/z: 419 [MH^+].
1H-NMR (500 MHz, DMSO) δ: 10.63 (s, 1 H), 8.65 (dd, 1H); 8.16 (dd, 1H), 7.42 (m, 1H); 6.89 (d, 1H); 6.85 (d, 1H); 6.7 (m, 2H); 6.79 (dd, 1H); 6.77 (d, 1H); 6.67 (d, 1H);

Example 8

6-[2-(4-Quinolin-8-yl)piperazin-1-yl)ethyl]-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt (E8)

The title compound (**E8**) was prepared in 20% yield according to the general procedure starting from 8-piperazin-1-ylquinoline (E8).

MS; (ES) m/z: 389.2[MH^+].

^{1}H-NMR (500 MHz, DMSO) δ: 10.64 (s, 1 H), 8.84 (dd, 1H); 8.26 (dd, 1H), 7.50 (m, 1H); 7.48 (d, 1H); 7.47 (d, 1H); 7.14 (dd, 1H); 6.86-6.7 (m, 3H); 4.5 (s, 2H); 3.36 (m, 4H); 2.70 (m, 6H); 2.55 (m, 2H).

Example 9

6-{2-[4-(1*H*-Indol-4-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt (E9)

The title compound was prepared in 22% yield according to the general procedure from 4-piperazin-1-yl-1*H*-indole.

MS; (ES) m/z: 377.3[MH^+].

^{1}H-NMR (500 MHz, DMSO) δ: 11.00 (s, 1 H),10.64 (s, 1H); 7.22 (t, 1H); 6.99 (d, 1H); 6.94 (t, 1H); 6.85 (d, 1H); 6.79 (dd, 1H); 6.77 (d, 1H); 6.43 (d, 1H); 6.35 (t, 1H); 4.51 (s, 2H); 3.15 (m, 4H); 2.67 (m, 6H); 2.56 (m, 2H).

Example 10

6-{2-[4-(7-Chloro-2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-7-fluoro-4*H*-benzo[1,4]oxazin-3-one (E10)

The title compound (**E10**) was prepared in 32% yield according to the general procedure starting from 7-chloro-2-methyl-5- piperazin-1-ylquinoline (**D9**) and 6-(2-chloroethyl)-7-fluoro-4*H*-benzo[1,4]oxazin-3-one (**D24**).

MS; (ES) m/z: 456.2 $[MH]^+$.

^{1}H-NMR (500 MHz, DMSO) δ: 11.40 (s, 1H); 10.86 (s, 1H); 8.73 (s, 1H): 7.96 (d, 1H); 7.72 (d, 1H); 7.04 (d, 1H); 6.95 (d, 1H); 6.83 (d, 1H); 4.58 (s, 2H); 3.71-3.52 (m, 4H); 3.52-3.38 (m, 6H); 3.32 (m, 2H); 3.09 (m, 2H); 2.84 (s, 3H).

Example 11

4-Methyl-6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt (E11)

A solution of 6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]-oxazin-3-one hydrochloride salt (**E1**) (56 mg, 0.13 mmol) in dry DMF (4 mL) was cooled to 0°C and 60% sodium hydride (21 mg; 4.0 eq) was added. The reaction mixture was stirred under nitrogen at 0°C for 40 minutes and then methyl iodide (9 □L) was added. The mixture was allowed to stir at 0°C for 1h, poured into a saturated aq. solution of ammonium chloride (4 mL) and extracted into ethyl acetate (3x3 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The residue was passed through a SCX cartridge and the resulting crude product was dissolved in DCM (2 mL) and treated with 2.0 M HCl in diethyl ether (1.1

eq). The mixture was stirred at 0°C for 30 min, then concentrated *in vacuo* to give the title compound (**E11**) as a yellow solid (32 mg; yield 55%).
MS; (ES) m/z 417.3 [MH^+]. $C_{25}H_{28}N_4O_2$.HCl requires 416.
^{1}H-NMR (500 MHz, DMSO) δ: 8.36 (d, 1 H), 7.69 (d, 1 H), 7.56 (t, 1H), 7.22 (d, 1 H), 7.05 (d, 1 H), 6.86 (m, 3 H), 4.57 (s, 2 H), 3.34 (s, 3 H), 3.12 (m, 4H), 2.85-2.75 (m, 6 H), 2.70 (m, 2 H), 2.70 (s, 3 H).

Example 12
6-{2-[4-(2-Methylquinolin-5-yl)piperazin-1-yl]ethanoyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt (E12)
2-Methyl-5-piperazin-1-yl-quinoline (**D3**) (50 mg, 0.22 mmol, 1.0 eq.) and 6-(2-chloroethanoyl)-4H-benzo[1,4]oxazin-3-one (65 mg, 0.29 mmol, 1.3 eq.) were added to a solution of N,N-diisopropylethylamine (1.0 mL) in dry acetonitrile (3 mL). The reaction mixture was stirred at reflux for 7 h, then allowed to cool to r.t. and concentrated *in vacuo*. The residue was dissolved in water (15 mL) and ethyl acetate (15 mL) and shaken. The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was passed through a SCX cartridge then purified by flash chromatography, eluting with 2% methanol in DCM. The resulting product was dissolved in methanol (3 mL) and treated with 1.25 M HCl in ethanol (1 mL). The mixture was stirred at r.t. for 0.5 h, then concentrated *in vacuo* to give the title compound (**E12**) as a yellow solid (56 mg, yield 56%).
MS; (ES) m/z: 417 [MH^+]. $C_{24}H_{24}N_4O_3$.HCl requires 416.
^{1}H-NMR (500 MHz, DMSO) δ: 11.03 (s, 1H), 10.6 (bs, 1H), 8.88 (bs, 1H), 7.94 (bs, 2H), 7.79 (bs, 1H), 7.67 (d, 1H), 7.54 (dd, 1H), 7.52 (s, 1H), 7.18 (d, 1H), 5.15 (bs, 2H), 4.75 (s, 2H), 3.8-3.5 (m, 4H), 2.88 (bs, 3H).

Example 13
6-{1-Hydroxy-2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt (E13)
A stirred suspension of 6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethanoyl}-4*H*-benzo[1.4]oxazin-3-one (**E12**) (47 mg, 0.10 mmol, 1.0 eq.) in dry ethanol (2 mL) was cooled to 0° and sodium borohydride (15 mg, 0.40 mmol, 4.0 eq) was added portionwise. The reaction mixture was stirred at 0° under nitrogen for 3 h. The reaction was quenched at r.t. with a saturated aq. solution of ammonium chloride (10 mL) and extracted into ethyl acetate (3x15 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography, eluting with 2% methanol in DCM. The resulting product was disolved in methanol (3 mL) and treated with 1.25 M HCl in ethanol (1 mL). The mixture was stirred at r.t. for 0.5 h, then concentrated *in vacuo* to give the title compound (**E13**) as a yellow solid (15 mg, yield 33%).
MS; (ES) m/z: 419 [MH^+]. $C_{24}H_{26}N_4O_3$.HCl requires 418.

^{1}H-NMR (500 MHz, DMSO) δ: 10.62 (s, 1H), 10.27 (bs, 1H), 8.63 (d, 1H), 7.80 (m, 2H), 7.58 (d, 1H), 7.32 (d, 1H), 7.04-6.90 (m, 3H), 5.15 (d, 1H), 4.55 (s, 2H), 3.75 (bm, 4H), 3.35 (bm, 5H), 3.30 (m, 2H), 2.78 (s, 3H).

Example 14

6-{2-[4-(2-Methyl-4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt (E14)

The title compound (**E14**) was prepared in 36% yield according to the general procedure starting from 2-Methyl-5-(3-methylpiperazin-1-yl)quinoline (**D13**).

MS; (ES) m/z: 417.2[MH^+].

^{1}H-NMR (500 MHz, DMSO) δ: 10.63 (s, 1H); 8.36 (d, 1H); 7.57 (m, 2H); 7.38 (d, 1H); 7.07 (dd, 1H); 6.84 (d, 1H); 6.80 (dd, 1H); 6.77 (d, 1H); 4.52 (s, 2H); 2.62 (s, 3H); 3.2 (m, 4H); 2.5 (m, 4H).

Example 15

6-{2-[3-Methyl-4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt (E15)

The title compound (E15) was prepared in 58% yield following the general procedure from 2-methyl-5-(2-methylpiperazin-1-yl)quinoline (**D14**).

MS; (ES) m/z: 417.3 [MH^+]. $C_{25}H_{28}N_4O_2$requires 416.52.

^{1}H NMR (500MHz, DMSO) δ: 12.27 (bs, 1H), 10.77 (s, 1H), 9.07 (bs, 1H), 8.09 (d, 1H), 7.98 (t, 1H), 7.82 (d, 1H), 7.64 (d, 1H), 6.91 (d, 1H), 6.83 (dd, 1H), 6.77 (d, 1H), 4.51 (s, 2H), 3.75 (m, 1H), 3.6-3.2 (m, 6H), 3.5 (m, 2H), 3.05 (m, 2H), 2.87 (s, 3H), 0.79 (d, 3H).

Example 16

6-{2-[2-Methyl-4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt (E16)

The title compound (**E16**) was prepared in 28% yield according to the general procedure starting from 2-methyl-5-(3-methylpiperazin-1-yl)quinazoline (**D15**).

MS; (ES) m/z: 418.4 [MH^+]. $C_{24}H_{27}N_5O_2$requires 417.52.

^{1}H NMR (500MHz, DMSO) δ: 10.74 (sa, 1H), 9.59 (s, 1H), 7.85 (t, 1H), 7.58 (d, 1H), 7.24 (d, 1H), 6.91-6.75 (m, 3H), 4.51 (s, 2H), 3.95 (m, 1H), 3.8-3.2 (m, 4H), 3.5 (m, 2H), 3.05 (m, 2H), 3 (m, 2H), 2.73 (s, 3H), 1.39 (d, 3H).

Example 17

6-{2-[4-(2-Methylquinolin-5-yl)-3,6-dihydro-2*H*-pyridin-1-yl]ethyl}-4H-benzo[1,4]oxazin-3-one (E17)

The title compound (**E17**) was prepared from 2-methyl-5-(1,2,3,6-tetrahydropyridin-4-yl]quinoline (**D17**) and 6-(2-chloro)ethyl-4H-benzo[1,4]oxazin-3-one (**D4**) according to the general procedure described above in 20% yield.

MS; (ES) m/z: 400[MH^+]. $C_{25}H_{28}N_3O_2$ requires 399.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 8.30 (br s, 1 H), 8.25 (d, 1 H), 7.88 (d, 1 H), 7.57 (t, 1 H), 7.15-7.25 (m, 2 H), 6.85 (m, 2 H), 6.65 (s, 1 H), 5.72 (m, 1 H), 4.55 (s, 2 H), 3.25 (m, 2 H), 2.70-2.90 (m, 6 H), 2.70 (s, 3 H), 2.55 (m, 2 H).

Example 18
6-{2-[4-(2-Methylquinolin-5-yl)piperidin-1-yl]ethyl}-4-H-benzo[1,4]oxazin-3-one hydrochloride salt (E18)
The title compound (**E18**) was prepared from 2-methyl-5-piperidin-4-ylquinoline (**D19**) and 6-(2-chloro)ethyl-4H-benzo[1,4]oxazin-3-one (**D4**) according to the general procedure described above in 31% yield.
MS; (ES) m/z: 402 [MH^+]. $C_{25}H_{27}N_3O_2$ requires 401.
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.25 (br s, 1 H), 8.25 (d, 1 H), 7.85 (d, 1 H), 7.57 (t, 1 H), 7.35 (d, 1 H), 7.25 (t, 1 H), 6.82 (m, 2 H), 6.65 (s, 1 H), 4.55 (s, 2 H), 3.05-3.30 (m, 3 H), 2.60-2.80 (m, 4 H), 2.70 (s, 3 H), 2.20-2.40 (m, 2 H), 1.90-2.15 (m, 4 H).

Example 19
6-{2-[4-(2-Methylquinolin-5-yl)-[1,4]diazepan-1-yl]ethyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloride salt (E19)
The title compound (**E19**) was prepared by the general procedure reported above in 60% yield starting from 5-[1,4]diazepan-1-yl-2-methylquinoline (**D21**).
MS; (ES) m/z: 417.3 [MH^+]. $C_{25}H_{28}N_4O_2$requires 416.52.
^{1}H NMR (500MHz, DMSO) δ: 12.27 (bs, 1H), 10.77 (s, 1H), 9.07 (bs, 1H), 8.09 (d, 1H), 7.98 (t, 1H), 7.82 (d, 1H), 7.64 (d, 1H), 6.91 (d, 1H), 6.83 (dd, 1H), 6.77 (d, 1H), 4.51 (s, 2H), 3.75 (m, 1H), 3.6-3.2 (m, 6H), 3.5 (m, 2H), 3.05 (m, 2H), 2.87 (s, 3H), 0.79 (d, 3H).

Example 20
6-{2-[4-(2-Methylquinazolin-5-yl)-[1,4]diazepan-1-yl]ethyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloride salt (E20)
The title compound (**E20**) was prepared in 32% yield by the general procedure reported above from 5-[1,4]-diazepan-1-yl-2-methylquinazoline (**D22**).
MS; (ES) m/z: 418.4 [MH^+]. $C_{24}H_{27}N_5O_2$requires 417.52.
^{1}H NMR (500MHz, DMSO) δ: 10.85 (sa, 1H), 10.78 (s, 1H), 9.63 (s, 1H), 7.87 (t, 1H), 7.52 (d, 1H), 7.24 (d, 1H), 6.92 (d, 1H), 6.85 (dd, 1H), 6.78 (d, 1H), 4.53 (s, 2H), 3.8-3.5 (m, 6H), 3.5-3.47 (m, 4H), 3.03 (m, 2H), 2.85 (s, 3H), 2.4-2.15 (m, 2H).

Example 21
7-Fluoro-6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt (E21)
The title compound (**E21**) was prepared according to the general alkylation procedure from 2-methyl-5-piperazin-1-ylquinoline (**D3**) and 6-(2-chloroethyl)-7-fluoro-4*H*-benzo[1,4]oxazin-3-one (**D24**).
MS; (ES) m/z: 421.2 [$MH]^+$. $C_{24}H_{25}FN_4O_2.HCl$ requires 420.

^{1}H-NMR (500 MHz, DMSO) δ: 10.90 (m, 2 H), 8.40 (bs, 1 H), 7.60 (m, 2 H), 7.40 (d, 1 H), 7.40 (d, 1 H), 7.10 (m, 1 H), 7.00 (d, 1 H), 4.60 (s, 2 H), 3.80-3.00 (m, 4 H), 3.10-2.80 (m, 8 H), 2.70 (s, 3 H).

Example 22

6-{3-[4-(2-Methylquinolin-5-yl)-piperazin-1-yl]-propyl}-4*H*-benzo[1,4]-oxa-zin-3-one acetic acid salt (E22)

A mixture of (4-{3-[4-(2-methylquinolin-5-yl)piperazin-1-yl]propyl}-2-nitro-phenoxy)-acetic acid methyl ester (**D29**) (0.19 g, 0.4 mmol) and iron (0.9 g) in glacial acetic acid (5 mL) was stirred vigorously at r.t. for 4h under argon. The reaction mixture was diluted with ethyl acetate (100 mL) and filtered through a Celite pad and washed with ethyl acetate. The fitrate and washings were combined, the solvent was evaporated and the residue was co-evaporated with toluene (2 x 30 mL). The product was purified by column chromatography on silica gel (eluting with a methanol-DCM gradient) to give the title compound (**E22**) as an acetic acid salt (0.13g, 71%); ^{1}H-NMR (500 MHz, $CDCl_3$), δ: 1.88 (2H, q, *J* 7.6 Hz), 2.52 (2H, br t, *J* 7.6 Hz), 2.62 (2H, t, *J* 7.6 Hz), 2.73 (3H, s), 2.77 (4H, br m), 3.14 (4H, br t, *J* 4.4 Hz), 4.60 (2H, s), 6.65 (1H, d, *J* 1.2 Hz), 6.82 (1H, dd, *J* 8.2 Hz, 1.6 Hz), 6.9 (1H, d, *J* 8.2 Hz), 7.08 (1H, d, *J* 7.6 Hz), 7.25 (1H, d, *J* 8.5 Hz), 7.58 (1H, t, *J* 7.9 Hz), 7.73 (1H, d, *J* 8.5 Hz), 8.10 (1H, br s), 8.37 (1H, d, *J* 8.5 Hz); MS: m/z (MH^+) = 417/418.

Example 23

6-{3-[4-(7-Fluoro-2-methylquinolin-5-yl)piperazin-1-yl]-propyl}-4*H*-benzo-[1,4]oxazin-3-one (E23)

The title compound (**E23**) was prepared as described in Example 22 from 7-fluoro-2-methyl-5-piperazin-1-ylquinoline (**D30**).

MS: m/z (MH^+) = 435/436.

^{1}H-NMR (400 MHz, $CDCl_3$) δ_H 1.80 (2H, br q, *J* 7.0 Hz), 2.44 (2H, br t, *J* 7.4 Hz), 2.55 (2H, t, *J* 7.4 Hz), 2.64 (3H, s), 2.69(4H, br s), 3.06 (4H, br s), 4.53 (2H, s), 6.59 (1H, t, *J* 8.0 Hz), 6.76 (1H, d, *J* 8.0 Hz,), 6.83 (1H, d, *J* 8.0 Hz,), 7.12 (1H, d, *J* 8.8 Hz), 7.27 (1H, dd, *J* 10.0 Hz, 2.4 Hz), 8.20 (1H, d, *J* 8.8 Hz), 8.37 (1H, br s).

Example 24

6-{3-[4-(2-Methylquinolin-5-yl)-piperazin-1-yl]-propanoyl}-4*H*-benzo[1,4]-oxa-zin-3-one hydrochloric acid salt (E24)

2-Methyl-5-piperazin-1-yl-quinoline (**D3**) (0.50 g, 2.20 mmol) and 6-(3-chloropropanonyl)-4H-benzo[1,4]oxazin-3-one (0.65 g, 2.86 mmol, 1.3 eq.) (C. R. Acad. Sci., Ser. C 1970, 270(19), 1601-4) were added to a solution of N,N-diisopropylethylamine (10 mL) in dry acetonitrile (30 mL). The reaction mixture was stirred at reflux for 7 h, then allowed to cool to r.t. and concentrated *in vacuo*. The residue was dissolved in water (50 mL) and ethyl acetate (50 mL) and shaken. The organic phase was separated, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was passed through a SCX cartridge, then purified by flash chromatography,

eluting with 3% methanol in DCM, to afford the title compound (**E24**) as a yellowish solid (0.81 g, 85%).
MS; (ES) m/z: 431 [MH^+]. $C_{25}H_{26}N_4O_3$ requires 430
^{1}H-NMR (500 MHz, DMSO) δ: 10.83 (bs, 1H), 8.34 (d, 1H), 7.67 (d, 1H), 7.58 (m, 2H), 7.51 (d, 1H), 7.37 (d, 1H), 7.09 (dd, 1H), 7.05 (d, 1H), 4.68 (s, 2H), 3.16 (t, 2H), 3.00 (bs, 4H), 2.70 (bs, 4H), 2.68 (t, 2H), 2.62 (s, 3H).

Example 25
6-{1-Hydroxy-3-[4-(2-methylquinolin-5-yl)-piperazin-1-yl]-propyl}-4*H*-benzo-[1,4]oxazin-3-one hydrochloric acid salt (E25)
A rred suspension of 6-{3-[4-(2-methylquinolin-5-yl)-piperazin-1-yl]-propanoyl}-4*H*-benzo[1,4]-oxa-zin-3-one hydrochloric acid salt (**E24**) (300 mg, 0.70 mmol) in dry methanol (10 mL) was cooled to 0° and sodium borohydride (106 mg, 2.8 mmol, 4.0 eq) was added portionwise. The reaction mixture was stirred at 0° under nitrogen for 4 h then quenched at r.t. with a saturated aq. solution of ammonium chloride (50 mL) and extracted into ethyl acetate (3x50 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography, eluting with 5% methanol in DCM, to give the title compound (**E25**) as a yellowish solid (266 mg, 88%).
MS; (ES) m/z: 433 [MH^+]. $C_{25}H_{28}N_4O_3$ requires 432.
^{1}H-NMR (300 MHz, DMSO) δ: 10.65 (s, 1H), 8.30 (d, 1H), 7.55 (m, 2H), 7.32 (d, 1H), 7.10 (m, 1H), 6.90 (s, 1H), 6.80 (s, 2H), 5.40 (bs, 1H), 4.60 (m, 1H), 4.50 (s, 2H), 3.30 (bm, 4H), 2.65 (bm, 4H), 2.60 (s, 3H), 1.75 (m, 2H).

Example 26
6-{(E)-3-[4-(2-Methylquinolin-5-yl)piperazin-1-yl]propenyl}-4*H*-benzo[1,4]-oxa-zin-3-one hydrochloric acid salt (E26)
A stirred suspension of 6-{1-hydroxy-3-[4-(2-methylquinolin-5-yl)-piperazin-1-yl]-propyl}-4*H*-benzo-[1,4]oxazin-3-one hydrochloric acid salt (**E25**) (50 mg, 0.116 mmol) and p-toluenesulfonic acid (110 mg, 0.58 mmol, 5.0 eq) in dry toluene (3 mL) was refluxed for 4 h. The reaction was quenched at r.t. with a saturated solution of sodium hydrogencarbonate (10 mL) and extracted into ethyl acetate (3x15 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash chromatography, eluting with 2% methanol in DCM, to give the title compound (**E26**) as a yellow solid (20 mg, 42%).
MS; (ES) m/z: 415 [MH^+]. $C_{25}H_{26}N_4O_2$ requires 414.
^{1}H-NMR (500 MHz, DMSO) δ: 10.69 (bs, 1H), 8.38 (d, 1H), 7.57 (m, 2H), 7.36 (d, 1H), 7.10 (d, 1H), 7.01 (dd, 1H), 6.94 (d, 1H), 6.88 (d, 1H), 6.51 (d, 1H), 6.15 (m, 1H), 4.55 (s, 2H), 3.19 (d, 2H), 3.03 (bm, 4H), 2.70 (bm, 4H), 2.62 (s, 3H).

Example 27

6-{4-[4-(2-Methylquinolin-5-yl)piperazin-1-yl]butyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloric acid salt (E27)

A mixture of 6-(4-chlorobutyl)-4*H*-benzo[1,4]oxazin-3-one (30 mg), 2-methylquinolylpiperazine (40 mg) , sodium iodide (35 mg), and sodium carbonate (50 mg) were suspended in methyl isobutyl ketone (4 mL). The reaction mixture was heated at 120°C for 6 h., cooled to r.t., diluted with ethyl acetate (10 mL), filtered and cncentrated to dryness. The oily residue was purified by flash chromatography eluting with a 97/3 mixture of DCM/methanol to afford the title compound as a free base which was converted to the corresponding hydrochloride salt (**E27**) (yield 40%) using a 1M solution of HCl in diethyl ether.

^{1}H-NMR (500 MHz, DMSO) δ: 10.55, (bs, 1H), 10.49 (s, 1H), 8.67 (d, 1H), 7.81 (m, 2H), 7.62 (d, 1H), 7.31 (d, 1H), 6.85 (d, 1H), 6.77 (m, 2H), 4.50 (s, 2H), 3.60 (m, 2H), 3.40 (m, 2H), 3.50-3.10 (m, 4H), 3.18 (m, 2H), 2.79 (s, 3H), 2.57 (t, 2H), 1.79 (m, 2H), 1.63 (m, 2H).

Example 28

6-{4-[4-(2-Methylquinolin-5-yl)piperazin-1-yl]-cyclohex-1-enyl}-4*H*-benzo[1,4]-oxazin-3-one hydrochloric acid salt (E28)

Glacial acetic acid (0.3 mL) was added to a stirred mixture of 6-(4-oxocyclohex-1-enyl)-4H-benzo[1,4]oxazin-3-one (**D32**) (58 mg, 0.24 mmol), 2-methyl-5-piperazin-1-yl-quinoline (**D3**) (82 mg, 0.36 mmol, 1.5 eq.) and sodium triacetoxyborohydride (76 mg, 0.36 mmol, 1.5 eq) in 1,2-dichloroethane (4 mL) at r.t. The reaction mixture was stirred at r.t. overnight, then quenched with a saturated aq. solution of sodium hydrogencarbonate (20 mL) and extracted with ethyl acetate (3x20 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was passed through a SCX cartridge, then purified by flash chromatography, eluting with 3% methanol in dichloromethane, to afford the title compound (**E28**) as a yellowish solid (7 mg, yield 6%).

MS; (ES) m/z: 455 [MH^+]. $C_{28}H_{30}N_4O_2$ requires 454.

^{1}H-NMR (500 MHz, DMSO) δ: 10.65 (s, 1H), 8.36 (d, 1H), 7.58 (m, 2H), 7.11 (dd, 1H),7.08 (d, 1H), 6.99 (dd, 1H), 6.92 (d, 1H), 6.89 (d, 1H), 6.0 (bs, 1H), 4.54 (s, 2H), 3.03 (bs, 4H), 2.84 (bs, 2H), 2.79 (bs, 2H), 2.62 (s, 3H), 2.62 (m, 1H), 2.48 (m, 1H), 2.40 (m, 2H), 2.2 (m, 2H), 1.55 (m, 1H).

Example 29

6-{4-[4-(2-Methylquinazolin-5-yl)piperazin-1-yl]butyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloric acid salt (E29)

A mixture of 6-(4-chlorobutyl)-4*H*-benzo[1,4]oxazin-3-one (30 mg), 2-methyl-5-piperazin-1-ylquinazoline (**D12**) (40 mg), 5-(2-methylquinazolyl)piperazine (35 mg) , sodium iodide (35 mg), and sodium carbonate (50 mg) were suspended in methyl isobutyl ketone (4 mL). The reaction mixture was heated at 120°C for 16 h., cooled to r.t., concentrated under reduced pressure, diluted with DCM (**50 ml**) and washed

with water (**25 ml**). The organic phase was separated and the solvent removed under reduced pressure to give an oily residue that was purified by flash cromatography eluting with DCM/methanol in a gradient system (100/0 to 50/50) to afford a crude mixture. The mixture was further purified by preparative HPLC using a reverse phase column [Waters X Terra C_{18} eluting with water + 0.1% TFA (solvent A)/ ACN + 0.1% TFA (solvent B), in gradient at 43 mL/min, flow] to give a solution containing the title compound. A 5% solution of sodium bicarbonate was added until a basic pH was obtained and the acetonitrile was removed under reduced pressure. The aqueous phase was extracted with DCM (3 x 15 mL). The combined organics were dried (Na_2SO_4) and evaporated under reduced pressure to afford the free base of the title compound which was converted into the corresponding hydrochloride salt (**E29**) (37 mg, 40%).

MS; (ES) m/z: 432 $[MH]^+$.

^{1}H-NMR (500 MHz, DMSO) δ: 10.35, (s, 1H), 9.58 (s, 1H), 9.49 (bs, 1H), 7.87 (t, 1H), 7.61 (d, 1H), 7.62 (d, 1H), 7.25 (d, 1H), 6.88 (d, 1H), 6.77 (m, 1H), 6.72 (d, 1H), 4.52 (s, 2H), 3.23 (m, 2H), 3.60-3.10 (m, 8H), 2.76 (s, 3H), 2.54 (m, 2H), 1.69 (m, 2H), 1.58 (m, 2H).

Example 30

6-{2-[4-(2-Methylquinolin-5-yl)piperazin-1-yl]ethoxy}-4-H-benzo[1,4]oxazin-3-one (E30)

The title compound (**E30**) was prepared from 2-methyl-5-piperazin-1-ylquinoline (**D3**) and 6-(2-bromoethoxy)-4*H*-benzo[1,4]oxazin-3-one (**D36**) according to the genearl procedure described for Example 1. Yield 68%.

MS; (ES) m/z: 419$[MH^+]$. $C_{24}H_{26}N_4O_3$ requires 418.

^{1}H-NMR (300 MHz, $CDCl_3$) δ: 9.50 (br s, 1 H), 8.35 (d, 1 H), 7.65 (d, 1 H), 7.55 (t, 1 H), 7.20 (d, 1 H), 7.00 (d, 1 H), 6.83 (d, 1 H), 6.45 (m, 2 H), 4.50 (s, 2 H), 4.05 (t, 2 H), 3,32 (t, 2 H), 3.05 (m, 2 H), 2.85 (m, 2 H), 2.80 (s, 3 H), 2.35 (m, 2 H), 2.00 (m, 2 H).

Example 31

4-Methyl-6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethoxy}-4-H-benzo[1,4]oxazin-3-one (E31)

A solution of 6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]-ethoxy}-4-H-benzo-[1,4]-oxazin-3-one (**E30**) (20 mg, 0.05 mmol) in DMF at 0°C under nitrogen was treated with sodium hydride(2 mg, 0.08 mmol) and stirred at 0°C for 15 min. Methyl iodide (0.01 mL, 0.16 mmol) was added and the solution allowed to warm to room temp. over 3 h. The reaction mixture was then partitioned between water (20 mL) and DCM (3x25 mL). The combined organics were dried (Na_2SO_4) and chromatographed (eluent 5% MeOH/CH_2Cl_2) to afford the title compound (**E31**) as a yellow oil (2 mg, 10%).

MS; (ES) m/z: 433 $[MH^+]$. $C_{25}H_{28}N_4O_3$ requires 432.

Example 32

7-Fluoro-6-{2-[4-(7-fluoro-2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloride salt (E32)

The title compound (**E32**) was prepared in 27% yield according to the general procedure starting from 7-fluoro-2-methyl-5-piperazin-1-ylquinoline (**D30**) and 6-(2-chloroethyl)-7-fluoro-4*H*-benzo[1,4]oxazin-3-one (**D24**).

MS; (ES) m/z: $[MH]^+$.439.2

^{1}H-NMR (500 MHz, DMSO) δ: 11.42 (s, 1H); 10.86 (s, 1H); 8.79 (d, 1H); 7.70 (d, 1H); 7.70 (d, 2H); 7.34 (d, 2H); 6.94 (d, 1H); 6.84 (d, 1H); 4.54 (s, 2H); 3.69-3.54 (m, 4H); 3.5-3.35 (m, 4H); 3.32 (m, 2H); 3.10 (m, 2H); 2.85 (s, 3H).

Example 33

6-{2-[4-(7-fluoro-2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloride salt (E33)

The title compound (**E33**) was prepared in 30% yield according to the general procedure starting from 7-fluoro-2-methyl-5-piperazin-1-ylquinoline (**D30**) and 6-(2-chloroethyl)-4*H*-benzo[1,4]oxazin-3-one (**D4**).

^{1}H-NMR (500 MHz, DMSO) δ:11.41 (s, 1H); 10.84 (s, 1H); 8.79 (d, 1H); 7.70 (d, 1H); 7.68 (d, 2H); 7.35 (d, 2H); 6.93 (d, 2H); 6.85 (d, 2H); 6.80 (s, 1H), 4.54 (s, 2H); 3.69-3.54 (m, 4H); 3.5-3.35 (m, 4H); 3.35 (m, 2H); 3.05 (m, 2H); 2.86 (s, 3H).

Example 34

7-Fluoro-6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethanoyl}-4*H*-benzo[1,4]oxazin-3-one (E34)

To a stirred suspension of 2-methyl-5-piperazin-1-ylquinoline (**D3**) (0.1g, 0.45 mmol) and 6-(2-chloroethanoyl)-7-fluoro-4*H*-benzo[1,4]oxazin-3-one (**D23**) (0.14 g, 0.585 mmol) in dry acetonitrile (6 mL), diisopropylethylamine (2 mL) was added. The mixture was refluxed for 7 h, then quenched with a saturated aq. solution of NH_4Cl (10 mL) and extracted with ethy acetate (3x10 mL). The organic phase was dried (sodium sulphate) and the solvent evaporated under vacuum. The residue was purified on SPE silica cartridge (DCM/methanol 95:5) to afford compound (**E34**) (0.058 g, 23%).

^{1}H-NMR (500 MHz, DMSO) δ: 10.9 (s, 1H); 8.4 (d, 1H); 7.6 (m, 2H), 7.4 (d, 1H); 7.4 (d, 1H); 7.1 (m, 1H); 7.0 (d, 1H);4.7 s, 2H); 3.8 (m, 2H); 3.1-2.8 (m, 8H); 2.6 (s, 3H).

Example 35

6-{1-Hydroxy-2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]-oxazin-3-one (E35)

To a stirred suspension of 7-fluoro-6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethanoyl}-4*H*-benzo[1,4]oxazin-3-one (**E34**) (0.058g, 0.134 mmol) in dry MeOH (5 mL) at 0°C $NaBH_4$ (0.02 g, 4eq) was added. The reaction mixture was stirred at 0°C for 5 h., then quenched with a saturated aq. solution of NH_4Cl (10 mL) and extracted with ethyl acetate (3x10 mL). The combined organics were dried over (sodium

sulphate), the solvent removed under vacuum and the crude purified on SPE silica cartridge (DCM to DCM/MeOH 95:5) to afford the title compound (**E35**) (0.028g, 48%).

MS; (ES) m/z: $[MH]^+$. 419.2

^{1}H-NMR (500 MHz, DMSO) δ:10.87 (s, 1H); 10.30 (s, 1H); 8.78 (s, 1H); 7.86 (s, 2H); 7.7 (s, 1H); 7.37 (s, 1H); 7.09 (d, 1H); 4.98 (m, 1H); 6.43 (s, 1H); 5.35 (m, 1H); 4.60 (s, 2H); 3.8-3.3 (m, 8H); 2.83 (s, 3H).

Example 36

6-{1-Methoxy-3-[4-(2-methylquinolin-5-yl)piperazin-1-yl]propyl}-4*H*-benzo[1,4]-oxazin-3-one (E36)

To a stirred suspension of 6-{1-hydroxy-3-[4-(2-methylquinolin-5-yl)-piperazin-1-yl]-propyl}-4*H*-benzo-[1,4]oxazin-3-one (**E25**) (50 mg, 0.12 mmol) in dry methanol (2 mL), trifluoroacetic acid (2 mL) was added. The reaction mixture was stirred atr.t. for 2 weeks. The solvent was concentrated *in vacuo* and the resulting crude product was passed through a SCX cartridge, then purified by flash chromatography, eluting with 5% methanol in DCM, to afford the title compound (**E36**) as a white solid (9 mg, yield 17%).

MS; (ES) m/z: 447 $[MH^+]$. $C_{26}H_{30}N_4O_3$ requires 446.

1H-NMR (300 MHz, DMSO) δ: 10.69 (s, 1H), 8.31 (d, 1H), 7.60 (m, 2H), 7.36 (d, 1H), 7.09 (d, 1H), 6.93-6.85 (m, 3H), 4.55 (s, 2H), 4.15 (t, 1H), 3.09 (s, 3H), 3.00 (s, 4H), 2.66-2.39 (s+m, 7H), 2.36 (q, 2H), 1.90-1.68 (m+m, 2H).

Example 37

6-{2-[4-(2-Methyl-1*H*-indol-4-yl)piperazin-1-yl]-ethyl}-4*H*-benzo-[1,4]oxazin-3-one hydrochloric acid salt (E37)

The title compound (**E37**) was prepared in 26% yield according to the general procedure from 2-methyl-4-piperazin-1-yl-1*H*-indole.

MS; (ES) m/z: 391.2$[MH^+]$.

^{1}H-NMR (500 MHz, DMSO) δ: 10.59 (s, 1 H),10.78 (s, 1H); 10.65 (s, 1H); 6.97 (d, 1H); 6.92 (t, 1H); 6.90 (d, 1H); 6.84 (dd, 1H); 6.78 (d, 1H); 6.46 (d, 1H); 6.12 (s, 1H); 4.54 (s, 2H); 3.66 (t, 2H); 3.65 (m, 2H); 3.3 (m, 4H); 3.10 (t, 2H); 3.0 (m, 2H); 2.35 (s, 3H).

Example 38

6-{2-[4-(5,6,7,8-Tetrahydronaphthalen-1-yl)piperazin-1-yl]ethyl}-4*H*-benzo-[1,4]oxazin-3-one (E38)

The title compound (**E38**) was prepared in 84% yield according to the general procedure from 1-(5,6,7,8-tetrahydronaphthalen-1-yl)piperazine.

MS; (ES) m/z: 392.2$[MH^+]$.

^{1}H-NMR (500 MHz, DMSO) δ: 10.79 (s, 1H); 10.64 (s, 1H); 7.08 (t, 1H); 6.92 (d, 1H); 6.85 (dd, 1H); 6.83 (m, 2H); 6.78 (d, 1H); 4.54 (s, 2H); 3.58 (d, 2H); 3.29 (m, 2H);

3.15 (d, 2H); 3.19 (m, 2H); 3.06 (m, 2H); 2.99 (m, 2H); 2.72 (m, 2H); 2.66(m, 2H); 1.71, m,, 4H).

Example 39

6-[2-(4-Naphthalen-1-ylpierazin-1-yl)ethyl]-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt (E39)

The title compound (**E39**) was prepared in 82% yield following the general procedure described above from 1-napthalen-1-ylpiperazine.

MS; (ES) m/z: 388.3 [MH^+]. $C_{24}H_{25}N_3O_2$requires 387.49

^{1}H NMR (500MHz, DMSO) δ: δ: 10.79 (s, 1H), 10.64 (bs, 1H), 8.13 (m, 1H), 7.93 (m, 1H), 7.68 (d, 1H), 7.54 (m, 2H), 7.48 (t, 1H), 7.21 (d, 1H), 6.96 (d, 1H), 6.87 (dd, 1H), 6.81 (d,1H), 4.56 (s, 2H), 3.68-3.46 (m/m, 2/2H), 3.46-3.21 (m/m, 2/2H), 3.38 (t, 2H), 3.03 (t, 2H).

Example 40

6-{1-Fluoro-2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]-oxazin-3-one (E40)

A stirred suspension of (**E13** free base) (100 mg, 0.24 mmol, 1.0 eq.) in dry DCM (4 ml) was cooled to 0° and DAST (48 uL, 0.36 mmol, 1.5 eq) was added dropwise. The reaction mixture was stirred at 0° under nitrogen for 1 h and at r.t. overnight. The reaction was quenched with a saturated aq. solution of sodium carbonate (20 mL) and extracted into dichloromethane (3x15 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography, eluting with 2% methanol in DCM to give the title compound (**E40**) as a yellow solid (75 mg, 75%).

MS; (ES) m/z: 421 [MH^+]. $C_{24}H_{25}FN_4O_2$ requires 420.

^{1}H-NMR (500 MHz, DMSO) δ: 10.76 (s, 1H), 8.32 (d, 1H), 7.57 (m, 2H), 7.37 (d, 1H), 7.10 (dd, 1H), 6.95 (m, 3H), 5.55 (m, 1H), 4.60 (s, 2H), 2.90 (s, 2H), 3.03 (m, 4H), 2.81 (m, 4H), 2.62 (s, 3H).

Example 41

6-{1-Fluoro-3-[4-(2-methylquinolin-5-yl)piperazin-1-yl]propyl}-4*H*-benzo[1,4]-oxazin-3-one (E41)

A stirred suspension of (**E25**) (50 mg, 0.116 mmol, 1.0 eq.) in dry DCM (2 ml) was cooled to 0° and DAST (23 uL, 0.174 mmol, 1.5 eq) was added dropwise. The reaction mixture was stirred at 0° under nitrogen for 1 h and at r.t. overnight. The reaction was quenched with a saturated aq. solution of sodium carbonate (10 mL) and extracted into DCM (3x15 mL). The organic layers were combined, dried (Na_2SO_4) and concentrated *in vacuo*. The crude product was purified by flash chromatography, eluting with 2% methanol in dichloromethane to give the title compound (E41) as a yellow solid (19 mg, 38%).

MS; (ES) m/z: 435 [MH^+]. $C_{25}H_{27}FN_4O_2$ requires 434.

^{1}H-NMR (300 MHz, DMSO) δ: 10.74 (s, 1H), 8.32 (d, 1H), 7.57 (m, 2H), 7.37 (d, 1H), 7.10 (dd, 1H), 6.95 (m, 3H), 5.55 (m, 1H), 4.57 (s, 2H), 3.02 (m, 4H), 2.65 (m, 4H), 2.60 (s, 3H), 2.50 (m, 2H), 2.40-1.90 (m, 2H).

Example 42

5-Fluoro-6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]-oxazin-3-one (E42)

6-(2-Chloroethyl)-5-fluoro-4*H*-benzo[1,4]oxazin-3-one (**D41**) (0.105 g, 0.46 mmol), sodium iodide (0.068 g, 0.46 mmol) and sodium carbonate (0.048 g, 0.46 mmol) were added to a solution of 2-methyl-5-piperazin-1-yl-quinoline (**D3**) (0.08 g, 0.35 mmol) in NMP (2.5 mL) at room temperature. The suspension was heated to 120°C for 3 h under nitrogen, then diluted with ethyl acetate (20 mL) and washed with water (2x 15 mL). The combined aqueous layers were back extracted with ethyl acetate (15 mL) and the combined organic layers were then washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Removal of the organic solvent under reduced pressure gave a crude which was purified by flash chromatography eluting with DCM, then 2-5% methanol in DCM, affording the title compound (**E42**) as a white solid (0.068 g, 46%).

MS; (ES) m/z 421.4 $[MH]^+$. $C_{24}H_{25}FN_4O_2$requires 420.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.20 (d, 1H), 7.80 (bs, 1H), 7.70 (d, 1H), 7.59 (t, 1H) 7.20 (d, 1H), 7.10 (d, 1H), 6.80 (t, 1H), 6.70 (d, 1H) 4.50 (s, 2H), 3.12 (m, 4H), 2.90 (m, 4H), 2.70 (s, 3H), 2.65 (m, 4H).

Example 43

5-Fluoro-4-methyl-6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]-oxazin-3-one (E43)

6-(2-Chloroethyl)-5-fluoro-4-methyl-4*H*-benzo[1,4]oxazin-3-one (**D42**) (0.080 g, 0.33 mmol), sodium iodide (0.049 g, 0.33 mmol) and sodium carbonate (0.035 g, 0.33 mmol) were added to a solution of 2-methyl-5-piperazin-1-yl-quinoline (**D3**) (0.097 g, 0.43 mmol) in NMP (2.5 mL) at room temperature. The suspension was heated to 120°C for 3 h under nitrogen, then diluted with ethyl acetate (20 mL) and washed with water (2x 15 mL). The combined aqueous layers were back extracted with ethyl acetate (15 mL) and the combined organic layers were then washed with brine (20 mL) and dried (Na_2SO_4). Removal of the organic solvent under reduced pressure gave a crude which was purified by flash chromatography eluting with DCM then 2% methanol in DCM to afford the title compound as a white solid (0.078 g, yield 55%).

MS; (ES) m/z 435.5 $[MH]^+$. $C_{25}H_{27}FN_4O_2$requires 434.

^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.35 (d, 1H), 7.70 (bs, 1H), 7.55 (t, 1H), 7.25 (d, 1H) 7.05 (d, 1H), 6.90(t, 1H), 6.75 (dd, 1H), 6.70 (d, 1H) 4.50 (s, 2H), 3.47 (d, 3H), 3.15 (m, 4H), 2,80 (m, 6H), 2,70 (m, 2H), 2,70 (s, 3H).

Example 44

6-{2-[4-(7-Chloro-2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4-methyl-4*H*-benzo-[1,4]-oxazin-3-one (E44)

The title compound (**E44**) was prepared according to the general procedure from 7-chloro-2-methyl-5-piperazin-1-ylquinoline (**D9**) and 6-(2-chloroethyl)-4-methyl-4*H*-benzo[1,4]oxazin-3-one (**D43**).

MS; (ES) m/z: 451.9 $[MH]^+$. $C_{25}H_{27}ClN_4O_2HCl$ requires 450.

^{1}H-NMR (500 MHz, DMSO) δ: 11.20 (bs, 1 H), 8.70 (d, 1 H), 7.92 (s, 1H), 7.69 (d, 1 H), 7.35 (s, 1 H), 7.13 (d, 1 H), 6.96 (m, 2 H), 4.63 (s, 3 H), 3.80-3.30 (m, 10 H), 3.30 (s, 3 H), 2.82 (s, 3 H).

Example 45

4-Ethyl-6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]-oxazin-3-one hydrochloride salt (E45)

The title compound (**E45**) was prepared according to the general procedure from 2-methyl-5-piperazin-1-ylquinoline (**D3**) and 6-(2-chloroethyl)-4-ethyl-4*H*-benzo-[1,4]oxazin-3-one **(D44)**. The free base was dissolved in DCM, HCl (1M solution in Et_2O) was added and the yellow solid thus obtained was washed with diethyl ether to give the HCl salt.

MS; (ES) m/z: 431 $[MH]^+$. $C_{26}H_{30}N_4O_2$ requires 430.

^{1}H-NMR of HCl salt (500 MHz, DMSO) δ: 10.69 (bs, 1H), 8.79 (bs, 1 H), 8-7.7 (3bs, 3 H), 7.35 (bs, 1 H), 7.16 (d, 1 H), 7.00 (d, 1 H), 6.96 (dd, 1 H), 4.61 (s, 2 H), 3.95 (q, 2 H), 3.7 (m, 2 H), 3.5-3.2 (m, 8 H+H2O), 3.10 (dd, 2 H), 2.83 (bs, 3H), 1.19 (t, 3H).

Example 46

6-{2-[4-(7-Fluoro-2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4-methyl-4*H*-benzo-[1,4]-oxazin-3-one hydrochloride salt (E46)

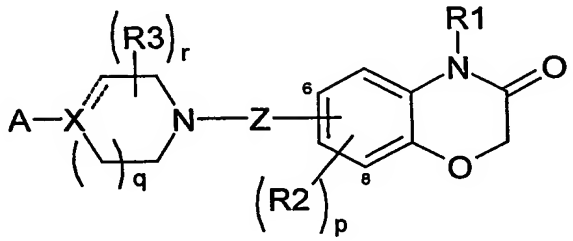
The title compound (**E46**) was prepared according to the general procedure from 7-fluoro-2-methyl-5-piperazin-1-ylquinoline (**D30**) and 6-(2-chloroethyl)-4-methyl-4*H*-benzo[1,4]oxazin-3-one (**D43**). The product was dissolved in DCM, HCl (1M solution in Et_2O) was added and the yellow solid thus obtained was washed with diethyl ether to give the HCl salt.

MS; (ES) m/z: 435 $[MH]^+$. $C_{25}H_{27F}N_4O_2$ requires 434.

^{1}H-NMR of HCl salt (500 MHz, DMSO) δ: 10.69 (bs, 1H), 8.56 (bs, 1 H), 7,57 (bs, 1H), 7,48 (bs, 1H, 7,25 (bs, 1H), 7.12 (d, 1 H), 6.98 (d, 1 H), 6.95 (dd, 1 H), 4.63 (s, 2 H), 3.7 (bm, 10 H), 3.3 (s, 3 H), 3.09 (dd, 2 H), 2.74 (bs, 3H).

Claims

1. A compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

A is a bicyclic 6,5 or 6,6 aromatic or heteroaromatic group which is optionally substituted by 1 - 4 substituents, which substituents may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, trifluoromethanesulfonyloxy, pentafluoroethyl, C_{1-6}alkoxy, arylC_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxyC_{1-6}alkyl, C_{3-7}cycloalkylC_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkylsulfonyl, arylsulfonyl, arylsulfonyloxy, C_{1-6}alkylsulfonamido, C_{1-6}alkylamido, Arylsulfonamido, arylcarboxamido, aroyl, arylC_{1-6}alkanoyl, and a group Ar^1-B, wherein B represents a single bond, O, S or CH_2 and Ar^1 represents a phenyl or a monocyclic heteroaromatic group, said Ar^1 group being optionally substituted by 1 - 3 substituents, which may be the same or different, and which are selected from the group consisting of a halogen, hydroxy, cyano, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkoxy or C_{1-6}alkanoyl;

R1 is hydrogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl or arylC_{1-6}alkyl;

R2 is independently halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy;

p is 0, 1 or 2;

R3 (a) is C_{1-6}alkyl and r is 0, 1, 2 or 3; or

(b) forms a bridge across the ring, the bridge consisting of a chain of 1 to 3 atoms, the bridge being optionally substituted by halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy; or

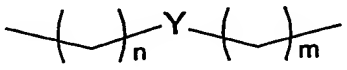
(c) is a chain of 1 to 3 atoms optionally substituted by halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy, the chain being attached to an available carbon atom in Z;

X is CH, N or C;

⎓ represents a single bond when X is CH or N; and ⎓ represents a double bond when X is C;

q is 1 or 2; and

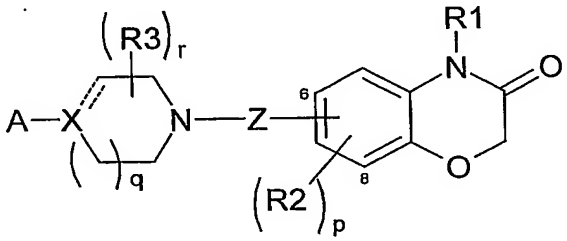
Z is attached to the 6-position or the 8-position of the benzoxazinone group and is a 3 to 7 membered cycloalkylene group , 3 to 7 membered cycloalkenylene group, -(CH=CH)- or a group



wherein m and n are independently 0, 1 or 2, and Y is a single bond, 3 to 7 membered cycloalkylene group, 3 to 7 membered cycloalkenylene group, -(CH=CH)- , -C(=O)-, -C(=CH_2)-, oxygen, or a methylene group optionally substituted by one or two groups selected from halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy;
provided that when A is naphthyl, 5,6,7,8-tetrahydronaphthyl or 2,3-dihydoindene, Z is not -(CH_2CH(OH))- , -(CH_2CH_2CH(OH))- or -(CH_2C(=O) .

2. A compound as claimed in claim 1, wherein A is a bicyclic 6,5 or 6,6 heteroaromatic group.

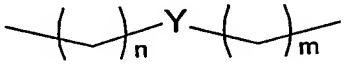
3. A compound of formula (Ia) or a pharmaceutically acceptable salt thereof:



(Ia)

wherein:
A is a bicyclic 6,5 or 6,6 heteroaromatic group which is optionally substituted by 1 - 4 substituents, which substituents may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, trifluoromethanesulfonyloxy, pentafluoroethyl, C_{1-6}alkoxy, arylC_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxyC_{1-6}alkyl, C_{3-7}cycloalkylC_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkylsulfonyl, arylsulfonyl, arylsulfonyloxy, C_{1-6}alkylsulfonamido, C_{1-6}alkylamido, Arylsulfonamido, arylcarboxamido, aroyl, arylC_{1-6}alkanoyl, and a group Ar^1-B, wherein B represents a single bond, O, S or CH_2 and Ar^1 represents a phenyl or a monocyclic heteroaromatic group, said Ar^1 group being optionally substituted by 1 - 3 substituents, which may be the same or different, and which are selected from the group consisting of a halogen, hydroxy, cyano, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkoxy or C_{1-6}alkanoyl;
R1 is hydrogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl or arylC_{1-6}alkyl;

R2 is independently halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy;
p is 0, 1 or 2;
R3 (a) is C_{1-6}alkyl and r is 0, 1, 2 or 3; or
(b) forms a bridge across the ring, the bridge consisting of a chain of 1 to 3 atoms, the bridge being optionally substituted by halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy; or
(c) is a chain of 1 to 3 atoms optionally substituted by halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy, the chain being attached to an available carbon atom in Z;
X is CH, N or C;
⚌ represents a single bond when X is CH or N; and ⚌ represents a double bond when X is C;
q is 1 or 2; and
Z is attached to the 6-position or the 8-position of the benzoxazinone group and is a 3 to 7 membered cycloalkylene group , 3 to 7 membered cycloalkenylene group, -(CH=CH)- or a group



wherein m and n are independently 0, 1 or 2, and Y is a single bond, 3 to 7 membered cycloalkylene group, 3 to 7 membered cycloalkenylene group, -(CH=CH)- , -C(=O)-, -C(=CH_2)-, oxygen, or a methylene group optionally substituted by one or two groups selected from halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy.

4. A compound as claimed in any of claims 1 to 3, wherein R1 is hydrogen or methyl.

5. A compound as claimed in any of claims 1 to 4, wherein R3 is methyl.

6. A compound as claimed in any of claims 1 to 5, wherein X is CH or N and ⚌ is a single bond.

7. A compound as claimed in any of claims 1 to 6, wherein q is 1.

8. A compound as claimed in any of claims 1 to 7, wherein Z is -$(CH_2)_2$-.

9. A compound as claimed in any of claims 1 to 8 , wherein A is indolyl, quinolyl, quinazolinyl or 2,3-dihydrobenzodioxinyl.

10. A compound as claimed in any of claims 1 to 9, wherein A is substituted by 1 to 4 substituents selected from the group consisting of halogen (particularly fluoro or

chloro), C_{1-6}alkyl (particularly methyl, ethyl and propyl), cyano, CF_3, C_{1-6}alkoxy (particularly methoxy, ethoxy or isopropoxy) or C_{1-6}alkanoyl.

11. A compound as claimed in any of claims 1 to 10, wherein A is selected from the group consisting of 5-quinolyl(2-Me), 5-quinolyl(2-Me, 7-Cl), 5-quinolyl(2-Me, 7-F) and 5-quinazolinyl(2-Me), 5-quinolyl(2-Me, 7-Me), 5-dihydrobenzo[1,4]dioxinyl, 8-quinolyl(6-methoxy), 8-quinolyl, 4-indolyl and 4-indolyl(2-Me).

12. A compound as claimed in claim 1, which is selected from the group consisting of:

6-{2-[4-(2-Methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt

6-{2-[4-(2,7-Dimethylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloride salt

6-{2-[4-(7-Chloro-2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloride salt

6-[2-(4-Quinolin-4-ylpiperazin-1-yl)ethyl]-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt

6-{2-[4-(2-Methylquinazolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt

6-{2-[4-(2,3-Dihydrobenzo[1,4]dioxin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt

6-{2-[4-(6-Methoxyquinolin-8-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt

6-[2-(4-Quinolin-8-yl)piperazin-1-yl)ethyl]-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt

6-{2-[4-(1*H*-Indol-4-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt

6-{2-[4-(7-Chloro-2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-7-fluoro-4*H*-benzo[1,4]oxazin-3-one

4-Methyl-6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt

6-{2-[4-(2-Methylquinolin-5-yl)piperazin-1-yl]ethanoyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt

6-{1-Hydroxy-2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt

6-{2-[4-(2-Methyl-4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt

6-{2-[3-Methyl-4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt

6-{2-[2-Methyl-4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt

6-{2-[4-(2-Methylquinolin-5-yl)-3,6-dihydro-2*H*-pyridin-1-yl]ethyl}-4H-benzo[1,4]oxazin-3-one

6-{2-[4-(2-Methylquinolin-5-yl)piperidin-1-yl]ethyl}-4-H-benzo[1,4]oxazin-3-one hydrochloride salt

6-{2-[4-(2-Methylquinolin-5-yl)-[1,4]diazepan-1-yl]ethyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloride salt

6-{2-[4-(2-Methylquinazolin-5-yl)-[1,4]diazepan-1-yl]ethyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloride salt

7-Fluoro-6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt

6-{3-[4-(2-Methylquinolin-5-yl)-piperazin-1-yl]-propyl}-4*H*-benzo[1,4]-oxa-zin-3-one acetic acid salt

6-{3-[4-(7-Fluoro-2-methylquinolin-5-yl)piperazin-1-yl]-propyl}-4*H*-benzo-[1,4]oxazin-3-one

6-{3-[4-(2-Methylquinolin-5-yl)-piperazin-1-yl]-propanoyl}-4*H*-benzo[1,4]-oxa-zin-3-one hydrochloric acid salt

6-{1-Hydroxy-3-[4-(2-methylquinolin-5-yl)-piperazin-1-yl]-propyl}-4*H*-benzo-[1,4]oxazin-3-one hydrochloric acid salt

6-{(E)-3-[4-(2-Methylquinolin-5-yl)piperazin-1-yl]propenyl}-4*H*-benzo[1,4]-oxa-zin-3-one hydrochloric acid salt

6-{4-[4-(2-Methylquinolin-5-yl)piperazin-1-yl]butyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloric acid salt

6-{4-[4-(2-Methylquinolin-5-yl)piperazin-1-yl]-cyclohex-1-enyl}-4*H*-benzo[1,4]-oxazin-3-one hydrochloric acid salt

6-{4-[4-(2-Methylquinazolin-5-yl)piperazin-1-yl]butyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloric acid salt

6-{2-[4-(2-Methylquinolin-5-yl)piperazin-1-yl]ethoxy}-4-H-benzo[1,4]oxazin-3-one

4-Methyl-6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethoxy}-4-H-benzo[1,4]oxazin-3-one

7-Fluoro-6-{2-[4-(7-fluoro-2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloride salt

6-{2-[4-(7-fluoro-2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]oxazin-3-one hydrochloride salt

7-Fluoro-6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethanoyl}-4*H*-benzo[1,4]oxazin-3-one

6-{1-Hydroxy-2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]-oxazin-3-one

6-{1-Methoxy-3-[4-(2-methylquinolin-5-yl)piperazin-1-yl]propyl}-4*H*-benzo[1,4]-oxazin-3-one

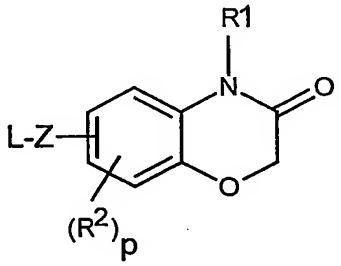
6-{2-[4-(2-Methyl-1*H*-indol-4-yl)piperazin-1-yl]-ethyl}-4*H*-benzo-[1,4]oxazin-3-one hydrochloric acid salt

6-{2-[4-(5,6,7,8-Tetrahydronaphthalen-1-yl)piperazin-1-yl]ethyl}-4*H*-benzo-[1,4]oxazin-3-one

6-[2-(4-Naphthalen-1-ylpierazin-1-yl)ethyl]-4*H*-benzo[1.4]oxazin-3-one hydrochloride salt
6-{1-Fluoro-2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]-oxazin-3-one
6-{1-Fluoro-3-[4-(2-methylquinolin-5-yl)piperazin-1-yl]propyl}-4*H*-benzo[1,4]-oxazin-3-one
5-Fluoro-6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1.4]-oxazin-3-one
5-Fluoro-4-methyl-6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]-oxazin-3-one
6-{2-[4-(7-Chloro-2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4-methyl-4*H*-benzo-[1,4]-oxazin-3-one
4-Ethyl-6-{2-[4-(2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4*H*-benzo[1,4]-oxazin-3-one hydrochloride salt
6-{2-[4-(7-Fluoro-2-methylquinolin-5-yl)piperazin-1-yl]ethyl}-4-methyl-4*H*-benzo-[1,4]-oxazin-3-one hydrochloride salt
and pharmaceutically acceptable salts thereof.

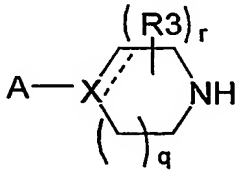
13. A process for the preparation of a compound of formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof, which process comprises:

(a) reacting a compound of formula (II):



(II)

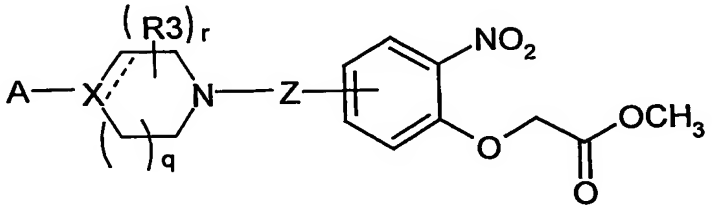
wherein R1, R2, p and Z are as defined in formula (I), and L is a leaving group, with a compound of formula (III):



(III)

wherein A, R3, ---, X, r and q are as defined in formula (I); or

(b) the reduction and concominant cyclisation of a compound of formula (IV):



(IV)

in which A, X, R3, ---, q, r and Z are as defined in formula (I);

and optionally thereafter for each of process (a) or (b):

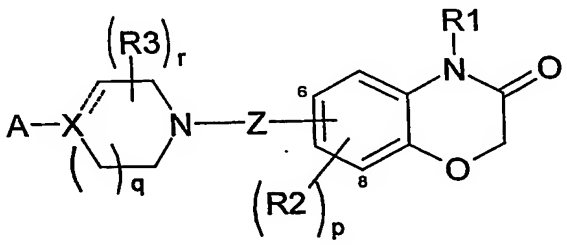
- removing any protecting groups, and/or
- converting a compound of formula (I) into another compound of formula (I), and/or
- forming a pharmaceutically acceptable salt.

14. A compound of formula (I) or formula (Ia) as defined in any of claims 1 to 12 or a pharmaceutically acceptable salt thereof, for use in therapy.

15. A pharmaceutical composition, which comprises a compound of formula (I) or formula (Ia) as defined in any of claims 1 to 12 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or excipient.

16. A process for preparing a pharmaceutical composition as defined in claim 15, the process comprising mixing a compound of formula (I) or formula (Ia) as defined in any of claims 1 to 12 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or excipient.

17. A compound of formula (Ib) or a pharmaceutically acceptable salt thereof:



(Ib)

wherein:

A is a bicyclic 6,5 or 6,6 aromatic or heteroaromatic group which is optionally substituted by 1 - 4 substituents, which substituents may be the same or different,

and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, C_{1-6}alkyl, trifluoromethanesulfonyloxy, pentafluoroethyl, C_{1-6}alkoxy, arylC_{1-6}alkoxy, C_{1-6}alkylthio, C_{1-6}alkoxyC_{1-6}alkyl, C_{3-7}cycloalkylC_{1-6}alkoxy, C_{1-6}alkanoyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkylsulfonyl, arylsulfonyl, arylsulfonyloxy, C_{1-6}alkylsulfonamido, C_{1-6}alkylamido, Arylsulfonamido, arylcarboxamido, aroyl, arylC_{1-6}alkanoyl, and a group Ar^1-B, wherein B represents a single bond, O, S or CH_2 and Ar^1 represents a phenyl or a monocyclic heteroaromatic group, said Ar^1 group being optionally substituted by 1 - 3 substituents, which may be the same or different, and which are selected from the group consisting of a halogen, hydroxy, cyano, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkoxy or C_{1-6}alkanoyl;

R1 is hydrogen, C_{1-6}alkyl, haloC_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-6}alkyl, C_{3-6}alkenyl, C_{3-6}alkynyl or arylC_{1-6}alkyl;

R2 is independently halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy;

p is 0, 1 or 2;

R3 (a) is C_{1-6}alkyl and r is 0, 1, 2 or 3; or

(b) forms a bridge across the ring, the bridge consisting of a chain of 1 to 3 atoms, the bridge being optionally substituted by halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy; or

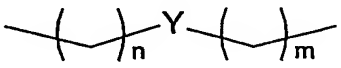
(c) is a chain of 1 to 3 atoms optionally substituted by halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy, the chain being attached to an available carbon atom in Z;

X is CH, N or C;

⋯⋯ represents a single bond when X is CH or N; and ═══ represents a double bond when X is C;

q is 1 or 2; and

Z is attached to the 6-position or the 8-position of the benzoxazinone group and is a 3 to 7 membered cycloalkylene group , 3 to 7 membered cycloalkenylene group, -(CH=CH)- or a group



wherein m and n are independently 0, 1 or 2, and Y is a single bond, 3 to 7 membered cycloalkylene group, 3 to 7 membered cycloalkenylene group, -(CH=CH)-, -C(=O)-, -C(=CH_2)-, oxygen, or a methylene group optionally substituted by one or two groups selected from halogen, C_{1-6}alkyl, cyano, haloC_{1-6}alkyl, C_{1-6}alkanoyl, C_{1-6}alkoxy or hydroxy;

for use in the treatment of a serotonin-related disorder.

18. A compound as claimed in claim 17, wherein the disorder is depression or anxiety.

19. Use of a compound of formula (Ib) as defined in claim 17 or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the treatment of a serotonin-related disorder.

20. The use as claimed in claim 19, wherein the disorder is depression or anxiety.

21. A method of treatment of a serotonin-related disorder, comprising administering to a mammal in need thereof a safe and effective amount of a compound of formula (Ib) as defined in claim 17 or a pharmaceutically acceptable salt thereof.

22. The method as claimed in claim 21, wherein the disorder is depression or anxiety.